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The American Journal of Medicine

Vol. XIII AUGUST, 1952 No. 2

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The Wolff-Parkinson-White Syndrome and Related Phenomena
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Clinical Studies

Difference in the Relation of Cardiac to Emetic Actions in Oral and Parenteral Digitalization
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This elaborate study of a minor point in digitalization indicates that, in general, more cardiac and less emetic effect is obtained with parenteral than with oral administration of digitalis preparations. The authors do not, however, recommend the parenteral route for ordinary digitalization.

Intramuscular Use of Pronestyl (Procaine Amide)
SAMUEL BELLET, STANLEY E. ZEEMAN AND STANTON A. HIRSH 145

Pronestyl has established value in the treatment of certain arrhythmias but may cause difficulties when administered by the rapid intravenous route. The authors find intramuscular injection of the gluconate or hydrochloride quite as effective and almost as prompt in action as the intravenously administered preparation and consider this the preferred route for parenteral use.

Infectious Mononucleosis . . . . . COLONEL ROBERT J. HOAGLAND 158

This report embodies a careful study of fifty-six cases of infectious mononucleosis and emphasizes the consistency of the clinical, hematologic and serologic picture if specific criteria for diagnosis are followed. What Dr. Hoagland says seems to make good sense.

Contents continued on page 5

in functional G.I. *distress*

though findings are negative, patients remain positive of their many symptoms – belching, flatulence, nausea, indigestion and constipation.

prompt and effective relief

can be given most of these patients by prescribing *Decholin/Belladonna* for alleviating spasm and stimulating liver function.

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reliable spasmolysis

The belladonna component of *Decholin/Belladonna* effectively relieves pain due to spasm and incoordinate peristalsis, and facilitates biliary and pancreatic drainage through relaxation of the sphincter of Oddi.

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Dehydrocholic acid *(Decholin)*, the most powerful *hydro*choleretic known, increases bile flow, flushes the biliary tract with thin fluid bile and provides mild laxation without catharsis.

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The American Journal of Medicine

Vol. XIII AUGUST, 1952 No. 2

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Infectious Mononucleosis. The Value of Differential Absorption Tests in Its Serologic Diagnosis . . . . . SIDNEY LEIBOWITZ 172

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A. YEOMANS AND G. H. STUECK, JR. 183

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Seminars on Gastrointestinal Physiology

Neural Regulation of Gastric and Intestinal Motility . . . . W. B. YOUMANS 209

Dr. Youmans contributes an authoritative analysis of present knowledge concerning neural regulation of motility of the gastrointestinal tract. After discussing the implications of experimental technics employing denervation, stimulation and use of relevant drugs, he concludes with a detailed description of intrinsic and extrinsic reflexes, commenting on clinical correlations as they arise.

Clinico-pathologic Conference

Progressive Visual Loss, Right-sided Weakness and Sudden Death 227

Clinico-pathologic Conference (Washington University School of Medicine)—This is a difficult and instructive case, well worth careful study. The discussion as to differential diagnosis is informative and helpful in the kind of problem, not too infrequent, presented by this patient.

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Hydergine — A New Product and New Approach To Peripheral Vascular Diseases

Investigation of a new approach to the treatment of peripheral vascular diseases and hypertension has established the practical value of hydrogenated ergot alkaloids.

Development of these alkaloids in the Sandoz Laboratories, study of their properties and evaluation of their usefulness by clinicians are the groundwork for the therapeutic application of Hydergine. Hydergine is an equiproportional mixture of dihydroergocornine, dihydroergocristine and dihydroergokryptine as methanesulfonates. These substances are produced by hydrogenation of several naturally-occurring alkaloids which comprise the ergotoxine group.*

Pharmacology and Therapeutics: The exceptional value of Hydergine in vascular diseases rests on its ability to attack these diseases through several actions. Lowering of peripheral resistance and vasodilatation result from an interplay of both central and peripheral actions:

a.) *centrally*—sedative effect and dampening of impulses from the vasomotor center.

b.) *peripherally* — adrenergic blockade (This enhances the centrally-induced effects.)

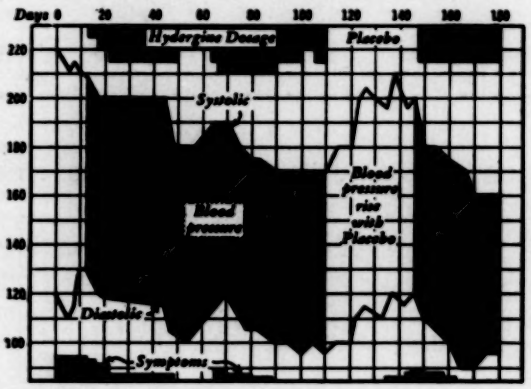
c.) *vagal stimulation*—resulting in bradycardia.

By reason of the latter action Hydergine is *free of the disadvantage which characterizes other adrenergic blocking agents,* namely the increase in heart rate which accompanies the administration of the latter agents.

In therapy of hypertension and/or vascular disease Hydergine affords a frank drop in blood pressure, relief of subjective symptoms and improvement of peripheral and coronary circulation; the slowing of heart rate allows more efficient diastolic filling

In some hypertensives the benefit obtained is largely from improvement of cerebral blood flow, thereby relieving subjective symptoms (tinnitus, dizziness, headache, visual disturbances etc.). This is often as important as a reduction of blood pressure.

Specific Indications: Hypertension; Raynaud's disease, acrocyanosis, frostbite; Buerger's disease, thrombophlebitis, arteriosclerosis obliterans.



Dosage and Administration:

Peripheral vascular disease: 1 to 2 cc. i.m. daily or every other day, according to need. Continue medication until clinical evidence of improvement.

Hypertension: First — preliminary injection test is given to determine what degree of therapeutic effect can be expected in the particular patient.

Procedure: have patient recline for 30 minutes; take a basic B.P. reading; inject 1 cc. Hydergine i.m. and note the degree and duration of drop in B.P. Marked response, lasting for several hours, is a sign of labile hypertension; a lesser response may indicate need for higher therapeutic dosage.

Therapeutic Dosage: if the test showed good response, start with 1 cc. i.m. 3 times per week. If test repsonse was slight, start with 1 to 2 cc. every one to two days. Dosage must be adjusted upward as necessary for each patient to obtain the optimal maintenance effect.

Form Available: Ampuls 1 cc., containing 0.3 mg. Hydergine.

*This term is no longer justified for these substances, since the chemical studies by Stoll have uncovered three distinct alkaloids (ergocornine, ergocristine and ergokryptine).

GENERAL REFERENCES:

1. NICKERSON, M.: J. Pharmacol. & Exper. Therap. *93:* 27, 1949. 2. STOLL, A. and HOFMANN, A.: Helvet. chim. acta *26:* 1570, 1943; ibid. 2070, 1943. 3. ROTHLIN, E.: Helvet. physiol. acta *2:* C 48, 1944. 4.ORTH, O. ET AL.: Federation Proc. *6:* 361, 1947. 5. FREIS, E. ET AL.: Am. J. M. Sc. *216:* 163, 1948. 6. BLUNTSCHLI, H. and GOETZ, R.: Am. Heart J. *35:* 873, 1948. 7. POPKIN, R.: California Med. *72:* 108, 1950. 8. JOSEPHS, I.: Am. Pract. *4:* 71, 1949.

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An instructive case discussed informatively.

Effects of Unilateral Renal Vein Hypertension Secondary to Splenorenal Vein Anastomosis on Individual Kidney Function

JONAS H. SIROTA AND ROBERT A. NABATOFF 242

The authors utilized the opportunity afforded by a case of splenorenal vein anastomosis to study the effects in the same subject of high and normal renal vein pressures on discrete renal functions, particularly in regard to electrolyte and water excretion before and during salt-loading. The results of this ingenious experiment are of unusual interest.

Coexistence of Cushing's Syndrome and Internal Hydrocephalus Produced by a Cerebellar Tumor . . . . . K. R. CRISPELL AND WILLIAM PARSON 247

The coexistence of Cushing's syndrome with marked internal hydrocephalus due to cerebellar tumor in this patient again suggests a relationship between hypothalmus and pituitary function.

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.

An Outstanding New Treatment

for seborrheic dermatitis of the scalp

FOR YOUR Rx ONLY—This simple yet notably effective new treatment for seborrheic dermatitis of the scalp is SELSUN Sulfide Suspension. With SELSUN, a six-week treatment will usually restore the scalp to a healthy, scurf-free condition; then applications at intervals of one to four weeks will control both scaling and itching for most patients. Applied while washing the hair, then rinsed out. Leaves scalp clean and odorless, no oily residue to stain clothing or linens.

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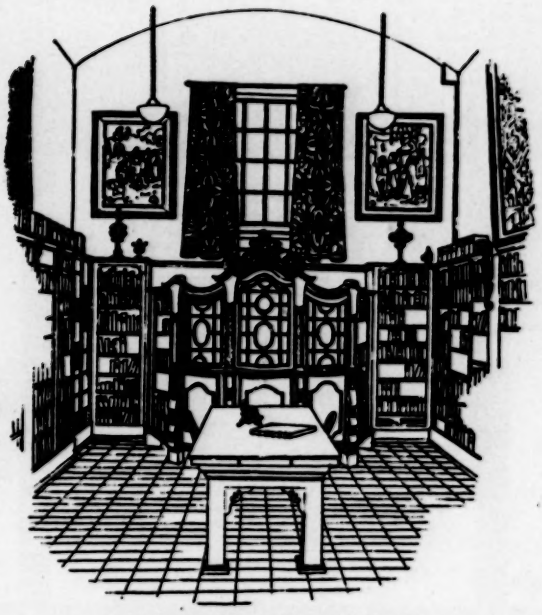
1. Slinger, W. N., and Hubbard, D. M. (1951), Arch. Dermat. & Syph., 64:41, July.
2. Slepyan, A. H. (1952), *Ibid.*, 65:228, February.
3. Ruch, D. M. (1951), Communication to Abbott Laboratories.
4. Kehoe, R. A. (1946; 1947), Communication to Abbott Laboratories.
5. Sterner, J. H., and Lidfeldt, V. (1941), J. Pharmacol. & Exper. Therap., 73:205, October.

New aureomycin minimal dosage for adults —four 250 mg. capsules daily, with milk.



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Hydrochloride Crystalline

because Aureomycin concentration is much higher in the urine than in the blood, so that very satisfactory therapeutic urinary levels may be reached with moderate oral dosage.

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Pyelonephritis

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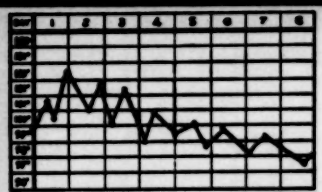
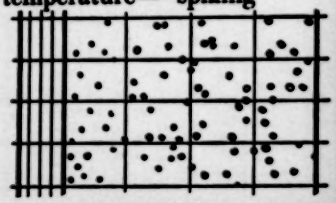
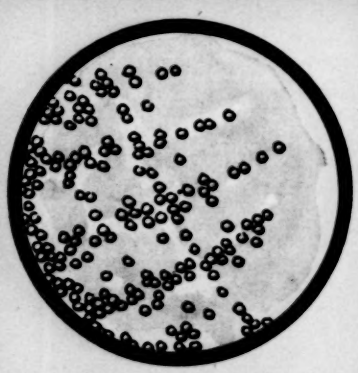


. . . temperature—"spiking"



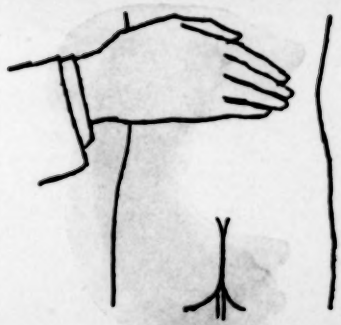
. . . white cell count—high

look for *clumps* of white cells in *catheterized* specimens



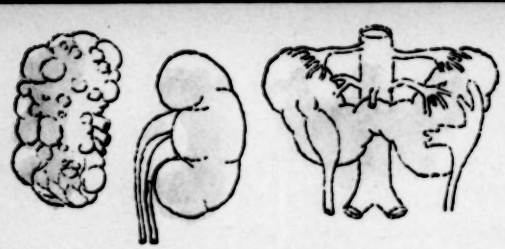
in 8 out of 10 children, colon bacillus invades

try the McKnight punch, or



palpation in C-V angle

suggestive of an acute abdomen



in children, 75% have congenital malformation . . . others may have calculus, foreign body, neoplasm, ureteral spasm.

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as well as other infections
rapidly respond to therapy
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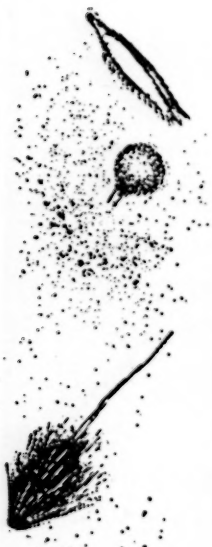

Piromen alleviates the immediate symptoms of pollenosis, and maintains effective control. Even cases which have failed to show improvement to desensitization and antihistaminics usually respond promptly to the administration of PIROMEN.

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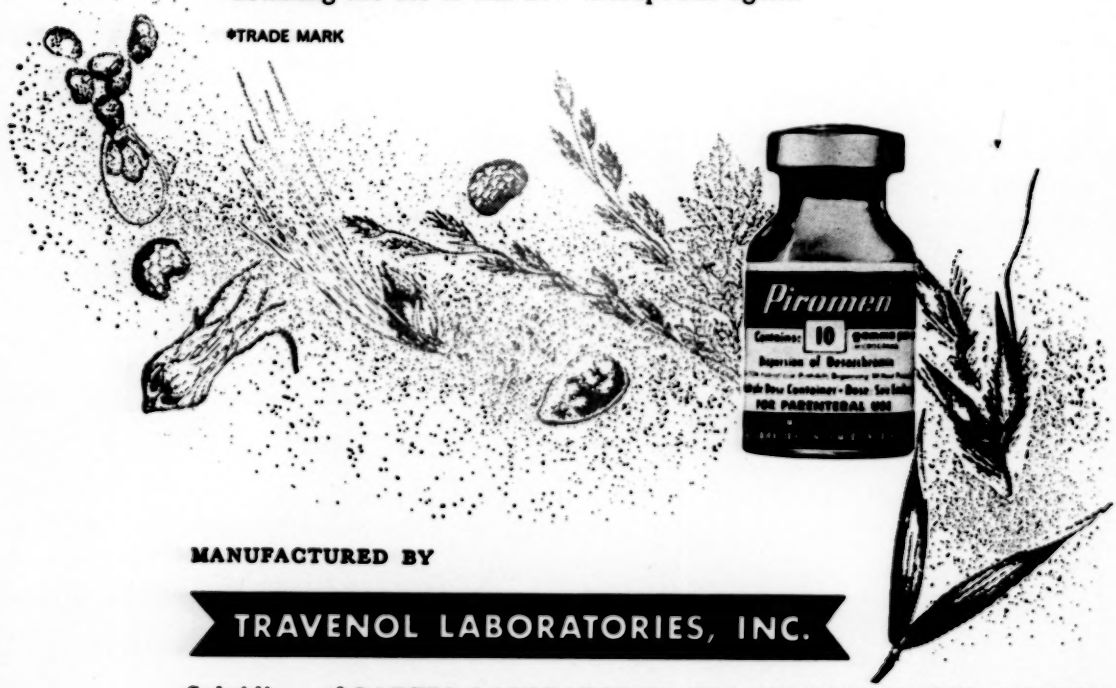

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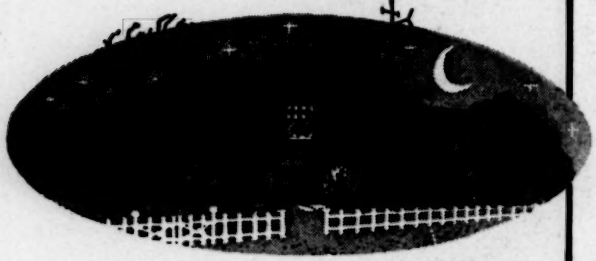

. . . sleeps poorly

. . . doesn't eat well

. . . is "always tired"

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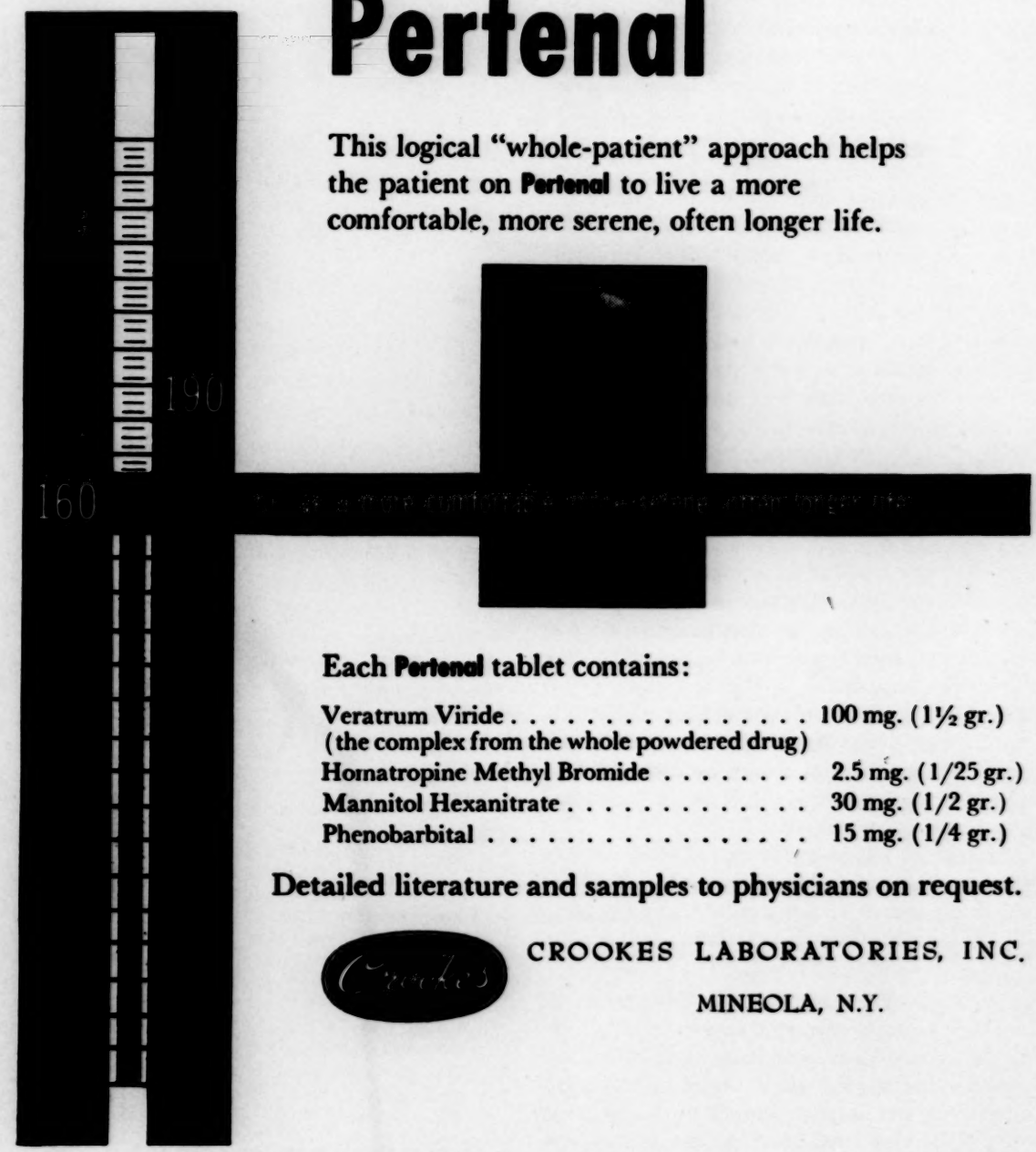

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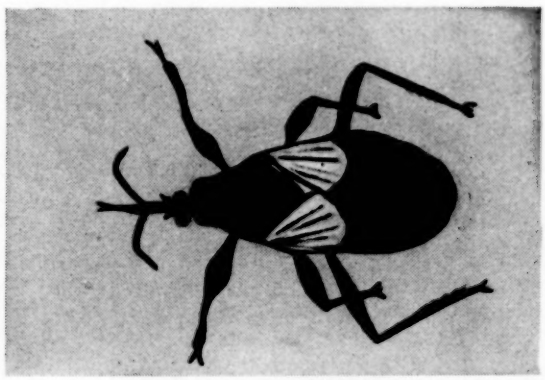
Nephenalin preferred to epinephrine, aludrine, for treatment of allergic crises

Two cases of severe allergic reactions to insect bites, "promptly controlled without the use of epinephrine," are described in a recent communication to the Letters of the International Correspondence Society of Allergists (Talley, J.B., Series XV, page 49). While the author does not wish to challenge the "life-saving effectiveness of epinephrine in treating anaphylactic reactions . . ." he points out that sublingual medication with Nephenalin (the unique, "relay-action" anti-asthmatic tablet) or with aludrine was "promptly effective . . . and they are much easier for the patient to have *immediately available* at all times . . . . Nephenalin is probably the better drug because of its immediate and prolonged action."

Assassin Bug Bite—The first patient, a farmer of 42, had awakened at 3 a.m. with severe itching and burning of the head, neck, and right forearm, and swelling of the ears, lips, and right forearm. Since he had a similar experience 1 year previously due to the bite of an assassin bug, and since there was a pinpoint puncture in the center of the right forearm edema, he searched his bed and found an assassin bug (which he brought to the office *alive* wrapped in a Kleenex tissue in his shirt pocket). At 7 a.m. the itching and edema were worse; severe headache was present; scattered hives, palpitation, and respiratory difficulty appeared; and on getting out of bed he found that he was too dizzy and weak to eat or work. That afternoon he was given 10 mg. of aludrine sublingually. In 5 minutes his symptoms had decreased markedly, and in 10 minutes he had no palpitation, respiratory difficulty, dizziness, or headache, but minor itching remained.

Wasp Sting—The second patient, a woman of 42, had been stung by a wasp 2 days previously. In 1 or 2 minutes she became dizzy, nauseated, and started vomiting. She was too weak to walk a few steps to her car. In 20 minutes her hands and feet were cold, blue, and swollen, and she became drowsy. Her symptoms decreased some by 10 p.m. —without benefit of any medical care—and she slept soundly that night. The weakness, nausea, drowsiness, and headache continued until she was seen 48 hours after the wasp sting. She was given a Nephenalin tablet sublingually for 5 minutes and then allowed to swallow it. In 1½ minutes there was marked decrease in the symptoms and in 10 minutes they had completely disappeared. She gave history of a similar but less severe wasp reaction 2 years previously.



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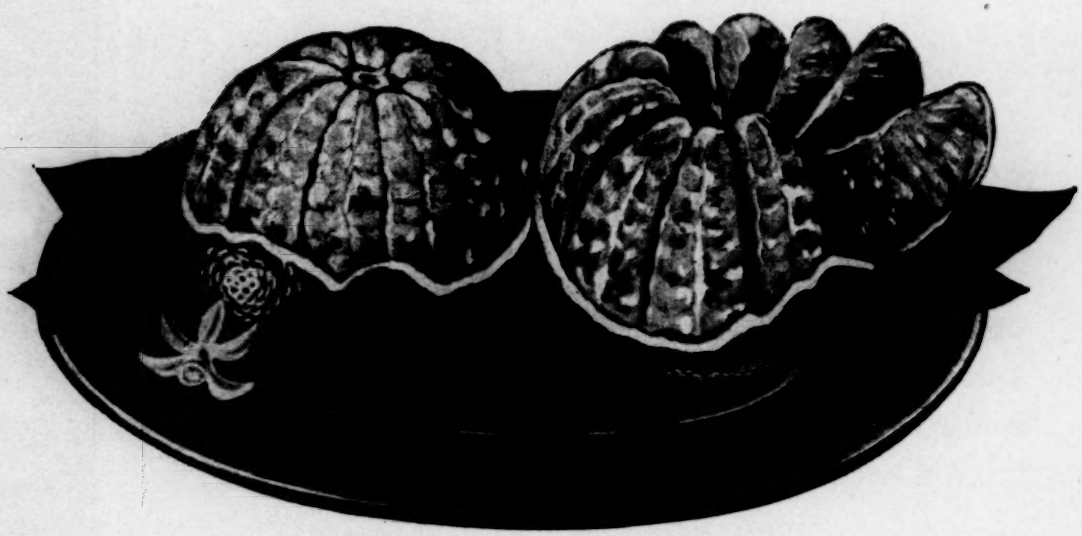

An Orange a Day for Better Nutrient Absorption

THE SIGNIFICANCE OF THE PROTOPECTINS

Human nutrition today means more than the mere ingestion of the chemical components of foodstuffs. While these nutrients—vitamins, minerals, proteins, fats, and carbohydrates—are needed to carry on metabolic life, food must also provide other substances required for normal functioning of many systems within the organism, particularly the gastrointestinal tract. Conversely, only in the optimally functioning digestive tract will released nutrients be absorbed to the greatest possible extent.

The Protopectins

Among such non-nutritive substances which aid in promoting better intestinal functioning are the protopectins, the subject of the present wide interest in complex carbohydrates.

Protopectins are the native form in which pectin occurs in certain fruits. California oranges supply generous amounts of these complex carbohydrates, which in the edible portion are contained in the fibrovascular bundles, the segmental walls, and the juice sacs; the juice contains comparatively little.

When the properly peeled fruit is eaten whole, the ingested protopectins—after conversion to pectin and subjection to enzymatic and bacterial action throughout the tract—yield substances largely responsible for their advantageous influence on intestinal function and nutrient absorption.

Improved Absorption of Nutrients

By lowering intestinal pH and lessening intestinal fermentation and putrefaction, the protopectins create an environment conducive to more complete absorption of important nutrients supplied by the daily diet. In this manner, absorption of non-caloric nutrients such as vitamins and minerals is enhanced, ***without leading to weight gain.*** The influence of the protopectins, of value at every age, is especially beneficial in the later years of life.

Other Benefits

Because of their demulcent influence the protopectins counteract the effects of intestinal irritants, thus aiding in the prevention of diarrhea. Through their water-binding power they lead to the formation of desirable gelatinous bulk which stimulates peristalsis and tends to prevent constipation. By lowering the intestinal pH, the protopectins tend to inhibit the growth of putrefactive and otherwise undesirable microorganisms present in the intestine.

These beneficial effects are over and above, and entirely separate from, the multiple vitamin values of oranges. Oranges remain the best practical source of vitamin C. Sunkist Oranges are the finest of the crop of California, where sunshine, mineral-rich soil, and cool nights combine to produce oranges of the highest quality.

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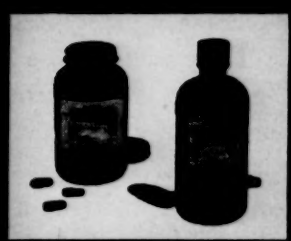

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1. Kirk, J. E.: Nutrition and Aging, Nutrition Rev. *9*:321 (Nov.) 1951.
2. Ohlson, M. A.; Roberts, P. H.; Joseph, S. A., and Nelson, P. M.: Dietary Practices of One Hundred Women from Forty to Seventy-Five Years of Age, J. Am. Dietet. A. *24*:286 (Apr.) 1948.
3. Kountz, W. B.; Hofstatter, L., and Ackermann, P.: Nitrogen Balance Studies in Elderly People, Geriatrics *2*:173 (May-June) 1947; Nitrogen Balance Studies Under Prolonged High Nitrogen Intake Levels in Elderly Individuals, ibid. *3*:171 (May-June) 1948.
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References:

1. Waterman, Hyman L. N.E.J. Med. 227: p. 736.
2. Unger, A. H., and Unger, L. G.P. 4:79 Dec. 1951
3. Unger, A. H., and Unger, L. Annals of Allergy (March-April) 1952

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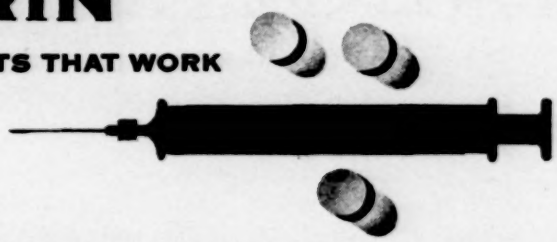

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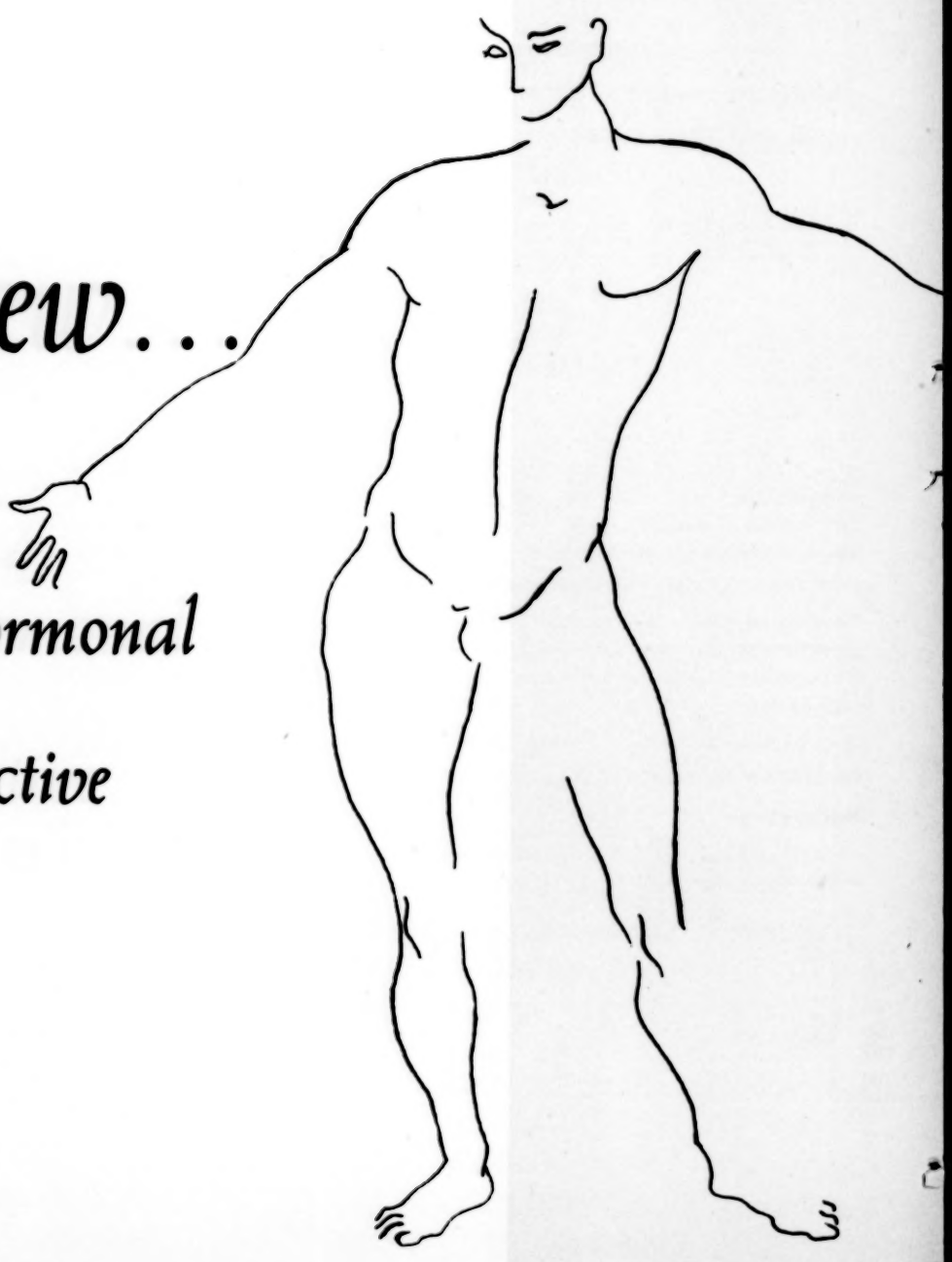

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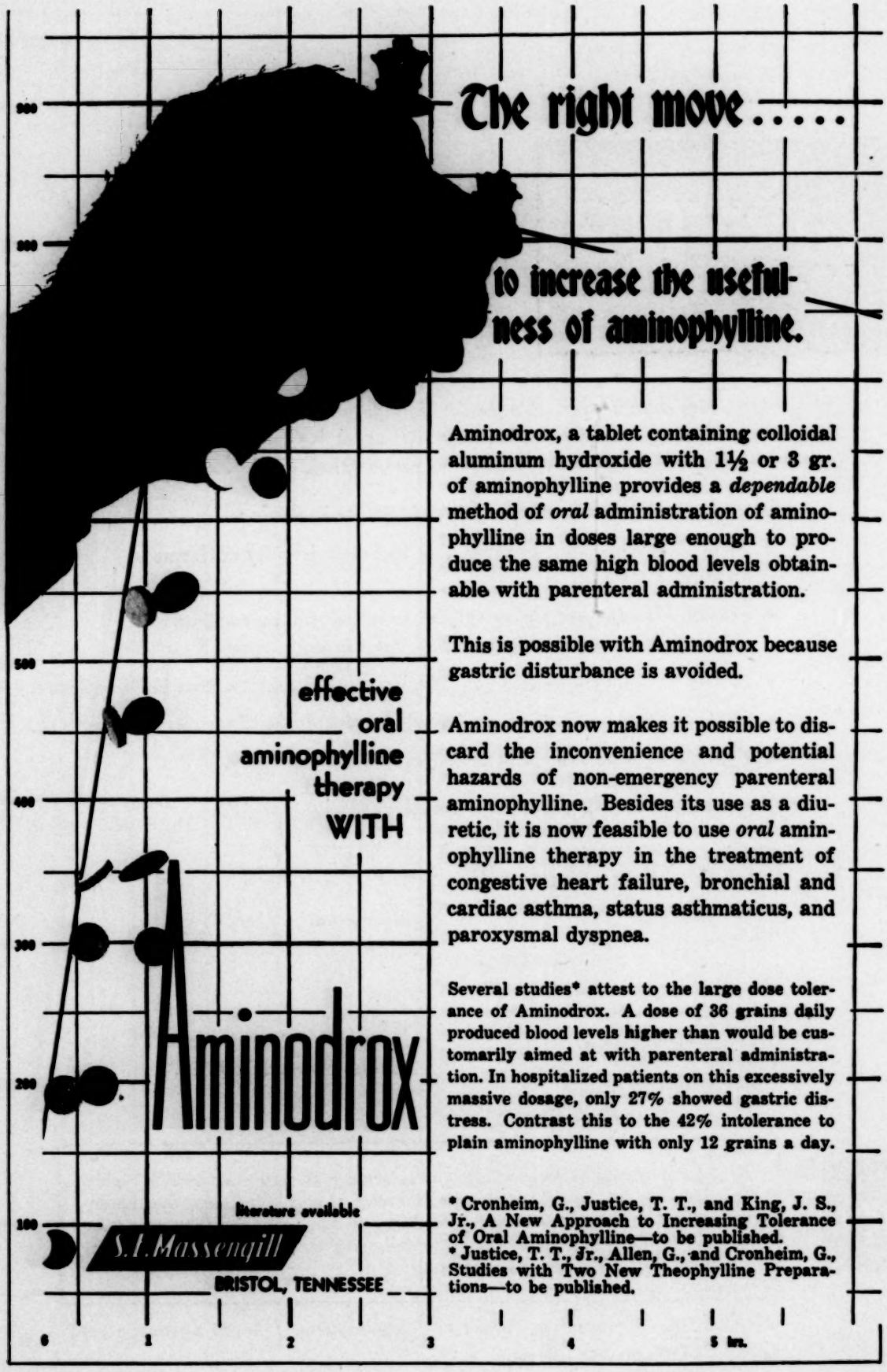
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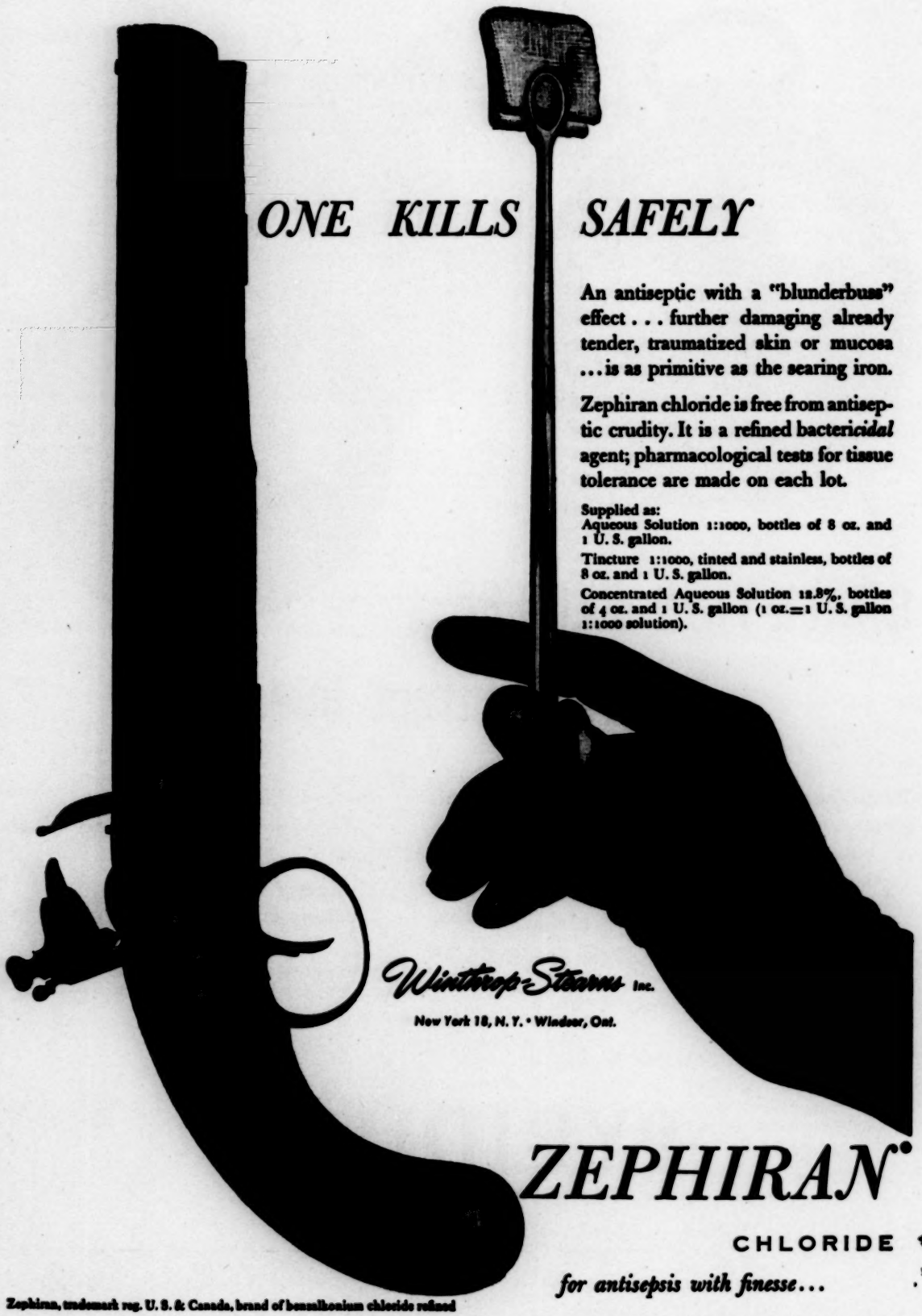

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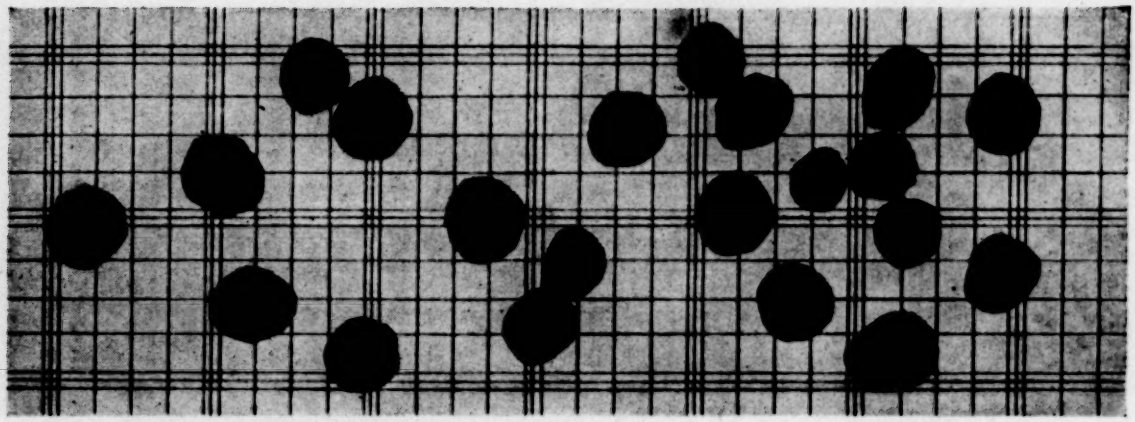

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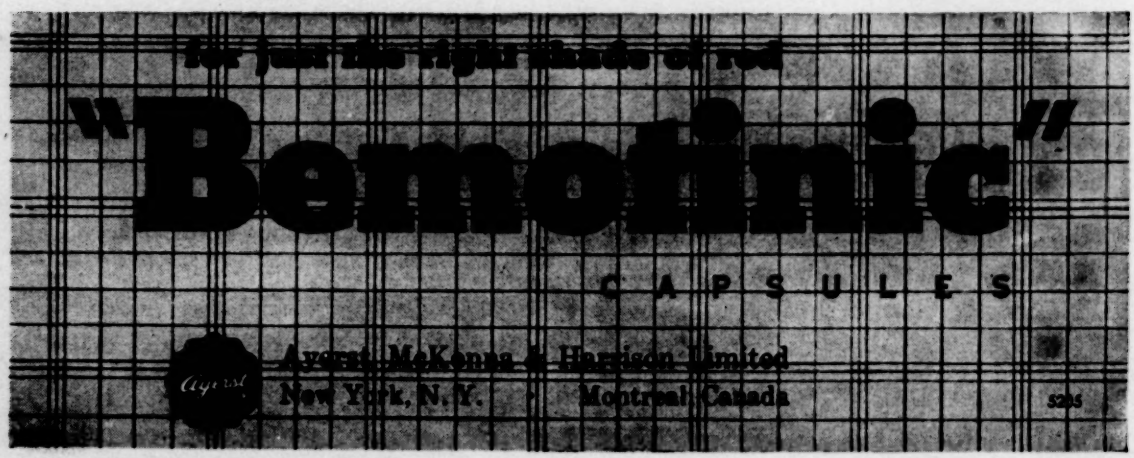

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The American Journal of Medicine

VOL. XIII AUGUST, 1952 No. 2

Editorial

The Wolff-Parkinson-White Syndrome and Related Phenomena

In 1930 Wolff, Parkinson and White[1] described a clinical syndrome consisting of electrocardiographic abnormalities characterized by short P-R intervals and widened, aberrant QRS complexes, often associated with paroxysms of supraventricular tachycardia. More recently, other paroxysmal supraventricular arrhythmias, extrasystoles, flutter and fibrillation, have been noted occasionally.[2] This disorder usually occurs in young individuals and has been thought to be congenital in origin.

Soon after the Wolff-Parkinson-White syndrome was described much speculation arose concerning the mechanism by which the aberrant complexes were produced. By 1944 Ohnell[3] was able to tabulate about forty different hypotheses which had been advanced, and subsequently at least ten more have been propounded. Nearly all these theories may be divided into two groups: (1) those which postulate that the auricular impulse in W-P-W complexes is carried to the ventricles by way of anomalous, accessory anatomic A-V connections; and (2) those which maintain that the impulse utilizes the normal conduction pathways in some abnormal manner. The theory which has gained the widest acceptance was first suggested by Holzman and Scherf,[4] and Wolferth and Wood,[5] who believed that the impulse passed from the auricles to the ventricles by way of the aberrant A-V bundle previously described by Kent. Subsequently, other anomalous anatomic A-V connections have been implicated. In this manner a short circuit bypassing the normal conduction system was provided and the short P-R interval and wide aberrant QRS complex became understandable. This idea was supported by the postmortem finding of Kent bundles in several cases of the W-P-W syndrome.[5,6] It gained further credence from the ingenious experiments of Butterworth and Poindexter,[7] who produced the aberration in animals by amplifying the electrical impulse derived from the auricles and passing it over a wire to the ventricle. Other investigators, including Ohnell[3] and Sodi-Pallares et al.,[8] also succeeded in producing W-P-W aberration in animals, and interpreted their results as indicating that anomalous anatomic A-V connections were responsible for the phenomenon. Thus the theory of aberrant bundles appeared to be based on fairly firm ground and the W-P-W syndrome became generally known as the "bundle of Kent syndrome."

Nevertheless, in many instances of the W-P-W syndrome careful histologic examination of the A-V border failed to reveal any evidence of accessory anatomic A-V connections.[9,10] In addition, it was not known whether such connections might not sometimes be present without the syndrome. Moreover, Kossmann et al.[11]

[1] WOLFF, L., PARKINSON, J. and WHITE, P. D. *Am. Heart J.*, 5: 685, 1930.

[2] FRIEDBERG, C. K. Diseases of the Heart. Philadelphia, 1949. W. B. Saunders Co.

[3] OHNELL, R. F. Pre-Excitation, a Cardiac Abnormality. Stockholm, 1944. A. A. Norstedt & Söner. Also, *Acta med. Scandinav.*, 152: 1, 1944.

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[9] OHNELL, R. F. *Cardiologia*, 4: 249, 1940.

[10] LEPESCHKIN, E. Modern Electrocardiography. Baltimore, 1951. Williams and Wilkins.

[11] KOSSMANN, C. E., BERGER, A. R., BRILLER, S. A., RADER, B. and BRUMLIK, J. *Circulation*, 1: 902, 1950.

noted the appearance of W-P-W complexes in two patients during cardiac catheterization. Thus although a certain amount of evidence could be adduced in favor of transmission of the impulse over the normal conduction system, the theory of anomalous bundles was not seriously challenged.

More recently, during the course of experimental studies on the auricular arrhythmias[12] it was noted that the aberrant ventricular complexes which sometimes occur with these arrhythmias were similar in many respects to those of W-P-W complexes. Later, W-P-W complexes were seen to appear in two patients during intrathoracic operations for bronchogenic carcinoma whenever the surgeon exerted traction on the pulmonary artery or auricular appendage. W-P-W aberration was observed to develop in several other patients following acute myocardial infarction involving the posterior wall of the heart. The same aberration was also noted in some dogs after experimental ligation of a coronary artery. The occurrence of W-P-W complexes in such a variety of apparently unrelated conditions seemed to preclude any explanation based on anomalous anatomic A-V bundles.

The need for direct experimental evidence appeared obvious and the problem has, therefore, been completely re-examined.[13] Some of the more recent experimental findings resulting from this study are as follows: First, it has been shown that all clinically recognized forms of W-P-W aberration can be produced in dogs by a wide variety of methods, notably by application of continuous direct electrical current of subthreshold intensity to the A-V node. When this current is modified so that its application makes the A-V node function as the pacemaker, all the supraventricular arrhythmias (extrasystoles, tachycardia, flutter and fibrillation) associated with the clinical W-P-W syndrome can be produced, depending upon the rate at which the new pacemaker is made to discharge. At relatively slow rates extrasystoles occur. When the rate is increased, tachycardia results and at rates of about 300 and 600, respectively, flutter and fibrillation are produced. Thus it appears that a disturbance in the A-V node could account for all the clinical manifestations of the congenital syndrome. It is to be noted that the occurrence of flutter and fibrillation in the W-P-W syndrome cannot be explained by the anomalous bundle theory, which attempts to explain the mechanism of tachycardia as a result of a 1:1 ventriculo-auricular rhythm. If the same mechanism were invoked to explain flutter and fibrillation, impossibly rapid ventricular rates would be required.

A more direct refutation of the theory of anomalous bundles has been provided by the observation that after cutting the bundle of His it was impossible to produce W-P-W aberration in dogs. This finding indicated clearly that the impulse in W-P-W complexes passes from auricles to ventricles over the normal conduction system and not over anomalous anatomical A-V pathways.

Studies by means of high-speed cinematography of the abnormal cardiac motions in W-P-W beats have revealed that the essential kinetic disturbance in these beats consists of a weak, premature, localized contraction of a part of one ventricle, followed by the normal contraction of the remainder of the ventricular mass at the normal time. By photographing the simultaneous electrocardiographic events on the same film with the cardiac motions a very close correlation between these phenomena was possible. This technic permitted the observation that the early slurred portion of the R wave in W-P-W complexes was related to the early localized contraction in one ventricle, while the rest of the R wave was associated with the normal contraction of the remainder of the ventricular musculature.

Considering that (1) the chief function of the A-V node is to delay the passage of the impulse from auricle to ventricle, (2) W-P-W aberration may be produced by altering the A-V node, (3) the impulse in W-P-W aberration utilizes the normal conduction system, (4) the aberrant and premature R wave is related to a premature localized contraction in one ventricle, and (5) that given cells of the A-V node seem to "supply" a specific region of the ventricle,[14] it is

[12] Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., Kruger, H. E., Fields, J., Flieg, W., Goldman, A., Karpman, H., Kennamer, S. R., Osborne, J. A., Sellers, A. L. and Smith, L. A. The Auricular Arrhythmias. Springfield, Ill., 1952. Charles C Thomas.

[13] Prinzmetal, M., Kennamer, R., Corday, E., Osborne, J. A., Fields, J. and Smith, L. A. Accelerated Conduction: The Wolff-Parkinson-White Syndrome and Related Conditions. New York. Grune & Stratton. In press.

[14] Smith, L. A., et al. Ventricular excitation in experimental bundle branch block. To be published.

reasonable to deduce that W-P-W aberration may result from a failure of part of the A-V node to delay the impulse normally in its passage through the node. Thus some of the impulse will arrive prematurely in a portion of one ventricle and depolarize it prematurely. This partial abolition of the normal delay may be termed "accelerated conduction."

The concept of a nodal disturbance as the factor responsible for W-P-W aberration has received support from the finding of a significant number of clinical cases in which the aberration was shown to have been acquired rather than congenital, and to have been associated with myocardial disease involving the A-V node. Three of these cases have come to autopsy. In two of them the area in or about the node was extensively involved by replacement fibrosis resulting from old infarcts, while in the third case the node was severely distorted by pressure from a fibrocalcific lesion, probably rheumatic in origin.[15] The remainder of the cases, which have not come to autopsy, were well substantiated instances of myocardial infarction affecting the posterior wall of the heart and presumably the A-V node.

As already mentioned, this disturbance might also be acquired from functional changes in the A-V node, such as those induced by the auricular arrhythmias or by traction on the auricular appendage or pulmonary artery.

Accelerated conduction can also result from disturbances in the ventricular myocardium, which probably setup a secondary disturbance in the node. Such cases have been seen clinically in patients with myocardial infarctions not involving the A-V node directly, in certain instances of "spontaneous" paroxysmal ventricular tachycardia[16] and fibrillation,[17] as a result of the action of certain drugs,[12] and in patients in whom the aberration develops during cardiac catheterization.[11] Accelerated conduction of this type, initiated by irritable ventricular foci, has been repeatedly produced experimentally in dogs.[13] Its mechanism is not understood.

The principle of accelerated conduction may thus be applied to a wide variety of clinical conditions. The W-P-W syndrome is only one of these and, incidentally, the only one which is congenital in origin. Especially common are those instances due to myocardial infarction, as any observer will see if he watches for such cases.

Many gaps in our knowledge of accelerated conduction still remain. The finding that this phenomenon can be produced in animals by stimulating the A-V node, and the discovery at autopsy of lesions in the node in three cases with accelerated conduction, while suggestive, are not conclusive evidence that all cases with this type of aberration are the result of a nodal disturbance. Much more experimental, clinical and pathologic study will be necessary in order to provide complete understanding of this interesting subject.

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Cedars of Lebanon Hospital and
Department of Medicine,
University of California School of Medicine,
Los Angeles, Calif.

[15] LANGENDORF, R., LEV, M. and PICK, R. Personal communication.

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[17] SCHWARTZ, S. P. and JEZER, A. *Am. J. M. Sc.*, 187: 473, 1934.

Clinical Studies

Difference in the Relation of Cardiac to Emetic Actions in Oral and Parenteral Digitalization*

HARRY GOLD, M.D., THEODORE GREINER, M.D., MCKEEN CATTELL, M.D., WALTER MODELL, M.D., JOSEPH GLUCK, M.D.,† RAYMOND MARSH, M.D.,‡ SYDNEY MATHES, M.D.,§ DEAN HUDSON, M.D.,** DONALD ROBERTSON, M.D.,** LEON WARSHAW, M.D., HAROLD OTTO, M.D., NATHANIEL KWIT, M.D. *and* MILTON KRAMER, M.D.

New York, New York

In a recent study[1] from our laboratory we reported an observation in cats which opened to question the prevailing belief concerning the site of action when vomiting results from the oral administration of digitalis. In these experiments oral doses of digitalis glycosides often produced vomiting under circumstances which suggested a "systemic" action, but which further experiments proved to be an action in the gastrointestinal tract. Such a phenomenon, if it occurs in man, would introduce a misleading factor in oral digitalization. An opportunity to test the point in man soon presented itself. There was the problem of a patient who had an ectopic auricular tachycardia. An oral course of a digitalis glycoside in doses given over a period of several days succeeded in restoring a normal rhythm, but it did so only when the drug was continued for a day or two after the onset of nausea and vomiting. Several days after the drug was discontinued the gastrointestinal symptoms disappeared, and soon thereafter the ectopic rhythm returned. The attempt to abolish the abnormal rhythm was repeated several times and with the same result, namely, a normal rhythm was restored, but only when the dosage reached a level beyond that causing gastrointestinal toxicity. With the suggestion from the animal experiments in mind, we gave the patient a series of doses of the same glycoside by intramuscular injection and, unlike the results with the oral courses, the normal rhythm was restored without gastrointestinal toxicity. This was also repeated several times, and also with the same results.

The practical importance of the observation that more action on the heart without gastrointestinal toxicity was possible by a parenteral than by the oral route seemed considerable, but it remained to be shown whether this experience represented a response peculiar to this patient or a basic difference between parenteral and oral digitalization which had not hitherto been recognized. Accordingly, a more extensive investigation was carried out in man to ascertain whether it is possible to secure greater cardiac actions without gastrointestinal toxicity by the use of the parenteral route than by the oral administration of the drug to the point of vomit-

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ing. The results form the subject of the present report.

METHOD

The experiments were carried out in ten patients. Their characteristics are summarized in Table 1.

and special note was made of the degree of cardiac action just prior to and at the level of the emetic dose. The drug was then discontinued until there was partial or complete recovery, when a series of parenteral doses was started and continued until the degree of cardiac action was the same as, or extended beyond

TABLE 1
CHARACTERISTICS OF PATIENTS IN THE STUDY

Patient	Age and Sex	Diagnosis	Drug and Corresponding Figure in Text
He.Mi.	59,F	Arteriosclerotic and hypertensive heart disease, enlarged heart, sinus rhythm	Digitoxin - 1, 2A,2B Digoxin - 8A,8B Lanatoside C - 12A,12B
Ro.Ad.	52,F	Rheumatic heart disease, mitral stenosis and insufficiency, enlarged heart, auricular fibrillation	Digitoxin - 3 Digoxin - 5
Be.Ma.	38,F	Unknown, ectopic auricular tachycardia	Digitoxin - 4A,4B
Ma.Do.	68,M	Arteriosclerotic heart disease,enlarged heart, auricular fibrillation	Digoxin - 6 Digoxin - 7
Be.Ho.	56,F	No heart disease, sinus rhythm	Digoxin - 9A,9B
Da.Le.	70,M	Arteriosclerotic heart disease, coronary thrombosis, sinus rhythm	Digoxin - 10A,10B
Ma.Sm.	59,F	Arteriosclerotic and hypertensive heart disease, enlarged heart, auricular fibrillation	Lanatoside C - 11
Ha.Lo.	60,F	Hypertensive heart disease, enlarged heart, sinus rhythm	Lanatoside C - 13A,13B
Be.Mc.	50,F	Arteriosclerotic and hypertensive heart disease, enlarged heart, sinus rhythm	Lanatoside C - 14A,14B
Ma.Si.	61,M	Arteriosclerotic and hypertensive heart disease, enlarged heart, sinus rhythm	Digifoline - 15A,15B

For the purpose of the experiment the patients were confined to bed in the hospital. The period varied from 2.5 to 21 weeks, average 6.5 weeks.

It was the general plan to digitalize the patient slowly with a series of oral doses until gastrointestinal toxicity was induced. The development of the cardiac action was observed

that in the oral course, or until vomiting resulted. Because of the fact that anorexia or nausea alone is sometimes inconclusive as evidence of digitalis toxicity, the doses were usually continued until vomiting appeared.

It is known that massive oral doses of digitalis or the glycosides of the digitalis series when given

at one time may cause vomiting by an action in the gastrointestinal tract,[2,3] but it is generally believed that after a slow course of relatively small oral doses the vomiting which results is brought on by a systemic action after absorption has taken place and that the site of action in this case is similar to that in parenteral digitalization.

The object was to administer enough during a protracted period to induce vomiting and to ascertain the intensity of the corresponding cardiac action. Since there is no knowledge as to whether the relation of the cardiac and emetic actions under these conditions might be influenced by the rate of digitalization, the systems of dosage and the total amounts of the drug were varied. It was necessary to have reasonable assurance that the amount of the drug was not substantially in excess of that necessary to bring on the particular effects. It was the plan to ascertain the maximal action on the heart that was obtainable with the level of dosage at the threshold for vomiting. It is probable that neither was actually attained but that, with the method used, both were closely approached. The usual practice was to give smaller doses parenterally than orally, and at shorter intervals parenterally than orally. The oral courses were administered during periods varying from eight to 264 hours, most of them from twenty-four to forty-eight hours, approximating standard regimens for digitalization with several doses given in a cumulative system.[4]

Four effects were used to measure the intensity of digitalis action on the heart, namely, change in the RT-T segment of the electrocardiogram, effect on the P-R interval, slowing of the apex rate in auricular fibrillation and abolition of an auricular ectopic tachycardia.

The effect of the drug on the RT-T segment of the electrocardiogram was employed in the patients with a normal sinus rhythm (seven experiments). Tracings were taken at varying intervals during the day, usually at intervals of two hours or less, when a course of digitalization was under way. The number of electrocardiograms in different experiments varied from thirty-five to 137, average seventy-five, approximately 600 in all. It was the object of taking such frequent electrocardiograms to enable us to determine the status of the RT-T change at any particular period or after any particular dose without having to depend in any case on only one tracing since substantial spontaneous variations in the height of the T wave and the shape of the R-T segment may occur without manifest cause. For the purpose of ranking the RT-T changes, each electrocardiogram was mounted on a 3 by 5 card with the legend on the back and a reader was used to whom the identity of the cards remained unknown prior to critical decisions. Both the oral and parenteral series were laid out on a table in the sequence the tracings were taken. The reader was presented with two cards, one from the oral series bearing the last tracing prior to the dose which was followed by emesis and the other from the parenteral series. His decision as to which of the two showed the greatest cardiac action was recorded. These cards were replaced in their position in the series and the reader examined several above and below in order to make certain that the two tracings were in no way peculiar and were representative of the sequence of changes in the respective series. The reader now proceeded to select the card showing the greatest cardiac action before the dose that was followed by vomiting. For the purpose of facility in charting, the rankings in the oral series were labeled in arbitrary units, 1+, 2+, etc., from the least to the greatest change. The cards of the parenteral series were then matched against these in order to assign similar values to tracings of the oral and parenteral series which showed similar degrees of change in the RT-T segment.

The effect on the P-R intervals as a measure of digitalis action was also employed in the patients with a normal sinus rhythm (six experiments). The readings were made from the same tracings used for the changes in the RT-T segments. The values for the P-R interval at any point in the experiment were based on the average of ten or more measurements.

Slowing of the apex rate in auricular fibrillation as a measure of the cardiac action was employed in five experiments. The technic was similar to that described in several previous studies[5,6] on the action of digitalis materials on the heart rate in auricular fibrillation. The patients were confined to bed, apex counts of one minute were made several times a day and the rate was observed until it leveled off. The course of oral doses was then started and counts were made at intervals of one or two hours until there was evidence of gastrointestinal toxicity. The patient was then allowed to go without digitalis until the apex rate returned approximately to the control level, when the digitalization was repeated with parenteral doses.

Gastrointestinal toxicity refers to a syndrome including several symptoms, usually persisting for hours: impaired appetite, severe nausea, general malaise, vomiting, and sometimes abdominal cramps and diarrhea. The term was never applied to equivocal symptoms in these experiments. Gastrointestinal toxicity was produced in twenty-four digitalizations, lasting an average of thirty-one hours with variations from three to 243 hours. In the course of these events there was vomiting in twenty of the digitalizations, vomiting recurring from time to time during an average period of nine hours, the number varying from one attack of vomiting to numerous attacks during a period of fifty-seven hours.

The fact that the plan of the experiments called for an oral course first raised the question whether response to the subsequent parenteral course might not in some way be influenced by the previous oral course. However, it so happened that all the patients had already received one or another kind of digitalis during varying periods of from months to years prior to their selection for the study, and in two of the ten patients the oral course was repeated. The effect of the second oral course showed the same qualitative relationship to the effect of the intravenous course as did the first oral course.

For the parenteral course the intramuscular route was used in three experiments, but because of uncertainty of absorption the intravenous route was employed for the majority.

Four members of the digitalis group were tested: digoxin (six experiments), lanatoside C (cedilanid) (four experiments), digitoxin (three experiments) and digifoline (one experiment). In all cases the same specimen of the drug was used for both the oral and parenteral courses.

RESULTS

A pair of digitalizations in one patient (an oral and parenteral) is referred to as one experiment. The results are based on fourteen such experiments, one in each of seven patients, two with two compounds in one patient, two with one compound in one patient and three with three compounds in one patient.

How to convey most satisfactorily the information supplied by these experiments presented something of a problem in view of the numerous variables. There were ten different patients, four different digitalis preparations, four different methods of measuring the cardiac action, wide differences in dosage regimens and changes in the electrocardiogram which require judgments with opportunities for differences of opinion. It was decided that crucial portions of each experiment in the form of a chart would provide the reader with means for judging the strength of the evidence on which our conclusions are based without unduly extending the length of this report. The results are therefore to be found in Figures 1 to 15.

General Legend. This should facilitate the inspection of the figures. In all charts the stippled blocks represent gastrointestinal toxicity in the oral course, the solid blocks in the parenteral course. The block labeled (v) refers to the period of vomiting, that above it usually anorexia and nausea, occasional abdominal cramps and/or diarrhea. In the curves from patients with auricular fibrillation the horizontal bar at the beginning shows the level of the heart rate at the end of the control period. The dots show the one-minute counts of the rate during the early hours after the doses. The circles represent the daily average of three or more counts. The vertical bar on these curves corresponds to the onset of gastrointestinal toxicity. In the figures of the patients with sinus rhythm the degree of effect on the RT-T segment is represented by the lines graded from 0 to 10+. They are an arbitrary device for charting a series of electrocardiograms which have been ranked with respect to the degree of change in the RT-T during the administration of a drug; for example, a 3+ line in an oral course represents the third distinguishable grade of RT-T change in a long series of tracings and one that is indistinguishable from a 3+ line in the parenteral course, but only when the same leads are compared in the two courses in the particular experiment in the same patient. The results are charted in pairs, lead I (oral and parenteral) and lead II (oral and parenteral). Both leads have been charted because, although in many cases either lead serves the purpose equally well, there are some in which one or the other shows the differences better. For each figure showing RT-T changes there is a corresponding figure with sample electrocardiograms from critical sections of the experiment which shows the reader the character of the changes represented by the graded lines. The letters above the lines correspond to the letters on the electrocardiograms. Unless otherwise stated at (*a*) is the control, at (*b*) the greatest cardiac action before the dose which

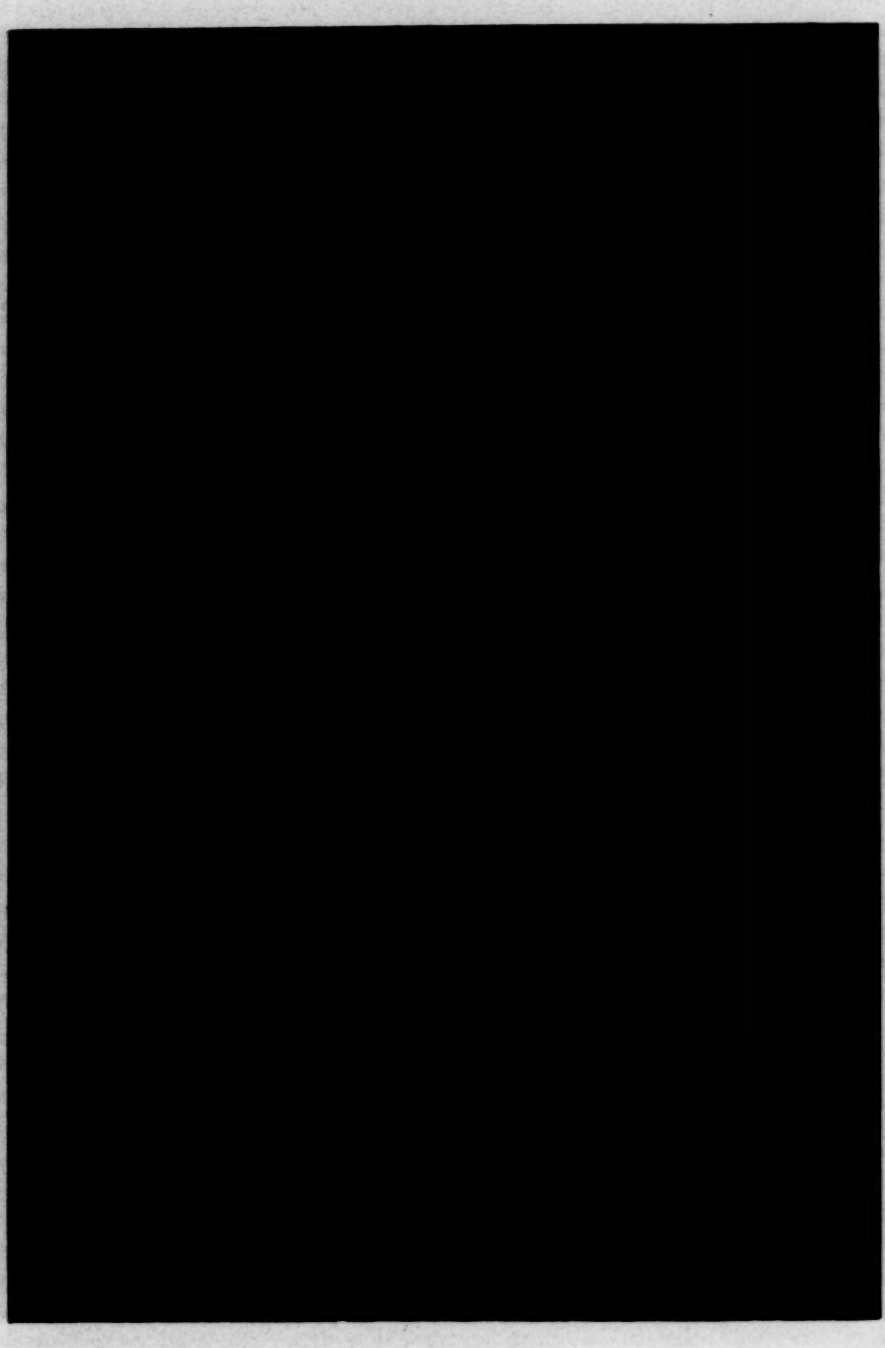
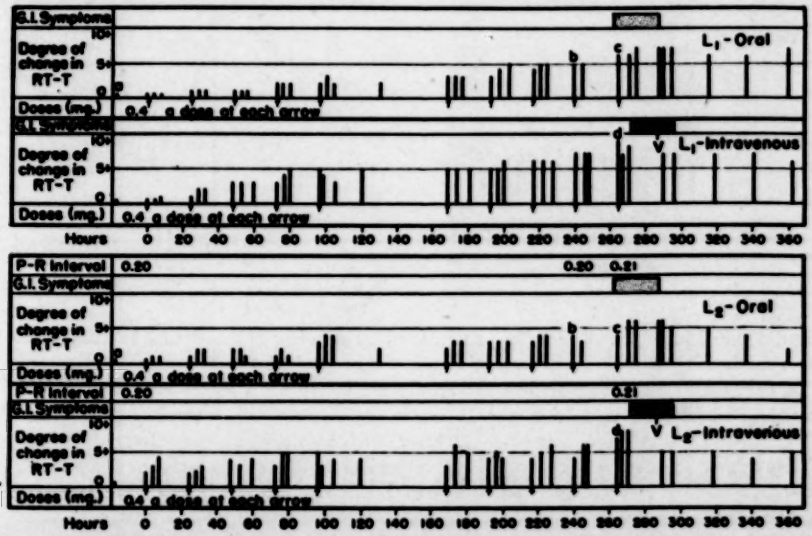


FIG. 1. Shows twenty-six consecutive tracings as a sample of the progressive changes in the RT-T segment during the course of oral digitalization by repeated doses during a period of 264 hours. The drug was digitoxin. A dose of 0.4 mg. was given after tracings 1, 3, 6, 8, 11, 14, 17, 19, 21 and 22. Tracing 26 was taken forty-eight hours after the last dose. Note that the sequence of the lowering of the T waves and depression of the R-T segments is not altogether regular, but the greater action with increasing dosage is unmistakable. The T wave may therefore serve for distinguishing degrees of action of the drug on the heart. Because of the instability of the RT-T the plan was adopted of using several electrocardiograms taken in a short period for judging the degree of digitalis action at any particular point. The graded lines which are used to represent the RT-T changes in the subsequent charts also show irregular variations. It is to be borne in mind that some of these fluctuations are not the result of the instability of the RT-T segments but are due to elimination of the drug. The intervals between doses were fairly regular during the day, but in the way these experiments were planned there was no need for continuing doses during the night and sometimes two days would elapse before the administration of doses was resumed. This would result in a series of RT-T patterns which involved not only the factor of instability of the RT-T segment, but also fluctuations in the amount of drug acting on the heart. To understand all subsequent figures refer to the general legend presented in the text. (P. 127.)

was followed with gastrointestinal toxicity in the oral course, at (*c*) the cardiac action at the time of gastrointestinal toxicity in the oral course, and at (*d*) the greatest cardiac action before the dose which was followed with gastrointestinal toxicity in the parenteral course. Deviations from this plan are indicated in the legends for each figure.

It will be noted in several of the figures that the intensity of the cardiac action increases after the beginning of the period of vomiting.* This may be due to continued absorption or further development of the cardiac action by the amount already absorbed. The intensity of the cardiac action shown under the vomiting blocks is to be ignored and only that portion prior to the vomiting block is to be considered, for the purpose of the study was to ascertain whether



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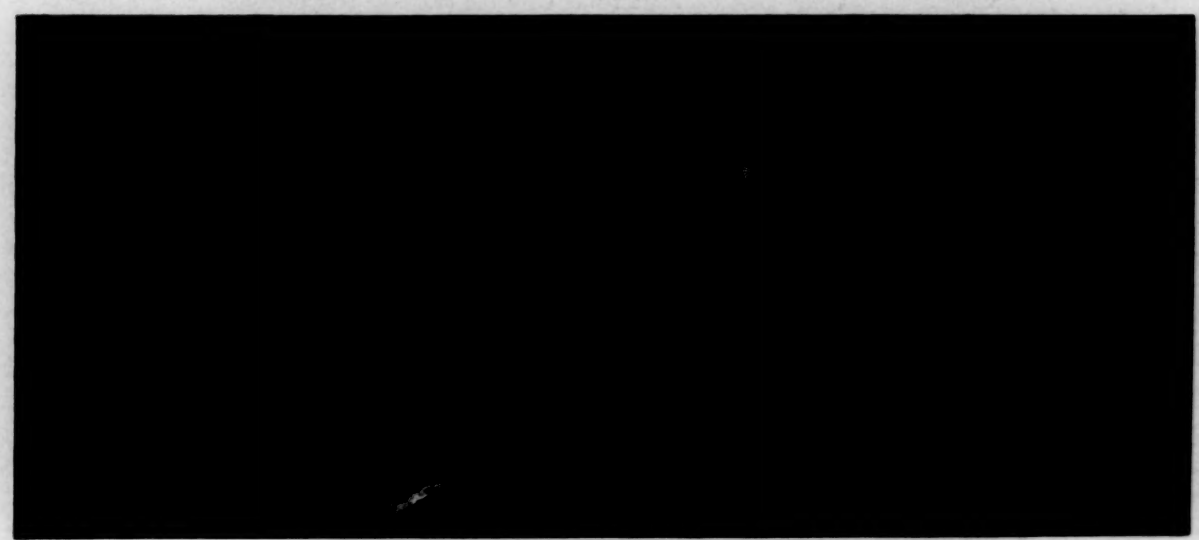


B

FIG. 2. A, digitoxin; cardiac action measured by changes in RT-T. The regimens of the oral and intravenous courses were identical; 0.4 mg. daily. In the oral course anorexia and nausea (no vomiting) began twenty-one hours after the ninth dose and lasted twenty-six hours. After an interval of thirty-one days the intravenous course was started. It caused gastrointestinal toxicity seven hours after the tenth dose, which lasted twenty-four hours with one bout of vomiting fifteen hours after the onset. Tracings were taken at intervals of four hours. Note the greater RT-T changes in the intravenous course long before doses which caused gastrointestinal toxicity. B, sample tracings of RT-T changes from experiment of Figure 2A. Note that in the intravenous course (*d*) the cardiac effect without gastrointestinal toxicity is greater than that in the oral course to the point of gastrointestinal toxicity (*c*).

It will be noted in several of the figures that the intensity of the cardiac action increases after

* In the text "vomiting" is used interchangeably with "gastrointestinal toxicity" to facilitate discussion.

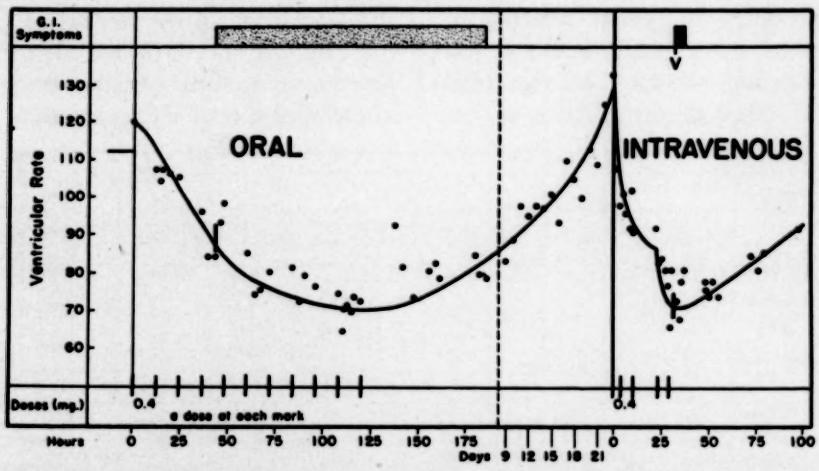


FIG. 3. Digitoxin; cardiac action measured by slowing of heart rate in auricular fibrillation. The oral course was given during a period of 120 hours, 11 doses of 0.4 mg. each. The dose which reduced the rate to 86 a minute caused severe anorexia and nausea, which persisted with additional doses for 160 hours (declined food for twenty-four hours). After an interval of twenty-three days the intravenous course was given during a period of 29 hours, 5 doses of 0.4 mg. each. Note that the dose which lowered the rate to 86 in the intravenous course, unlike the oral course, produced no gastrointestinal toxicity, and that the latter appeared only when the intensity of the cardiac action was much greater. This toxicity came on three hours after the last dose and persisted four hours.

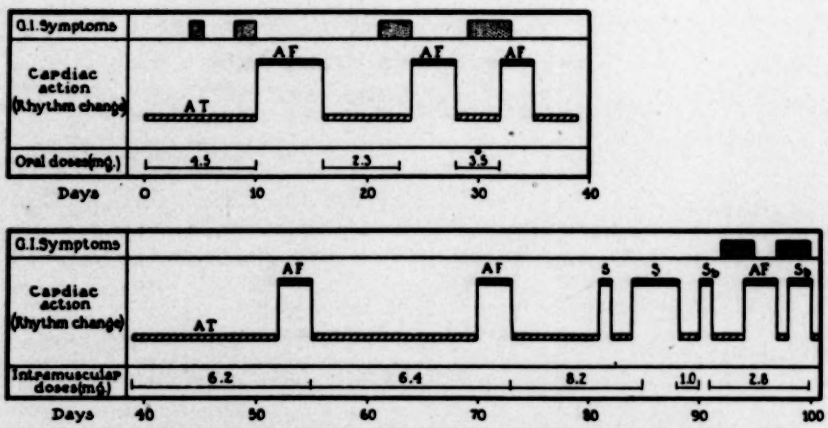


FIG. 4. A, digitoxin; cardiac action measured by conversion of ectopic auricular tachycardia to auricular fibrillation or sinus rhythm. For intramuscular injection a solution of digitaline nativelle in 5 per cent alcohol and 5 per cent sorbitan monolaurate (supplied by the Varick Pharmacal Company, Inc.) was used. AT, auricular tachycardia; AF, auricular fibrillation; S, sinus rhythm; S_b, sinus rhythm with block. Note that gastrointestinal toxicity (anorexia, nausea, vomiting) always preceded the change in rhythm when the drug was given by the oral route, whereas by the intramuscular route the cardiac effects were obtained without gastrointestinal toxicity. The vomiting at the end in the intramuscular course was probably the result of excessive cumulation. * Digoxin orally behaved in a similar manner.

it is possible to obtain the same degree of cardiac action *without* vomiting by the two routes of administration.

Evidence Supplied by Each of the Four Cardiac Actions. A careful examination of the figures and charts with the aid of points mentioned in the general legend will show that the degree of cardiac action at the threshold of gastrointestinal toxicity in the case of the oral courses is reproduced in the parenteral courses *without* gastrointestinal toxicity, and furthermore, that more cardiac action without vomiting is possible with the parenteral route of administration.

How much more action on the heart is possible without vomiting when the drug is given by the parenteral route than at the threshold of vomiting in the case of the oral route? We know of no direct or indirect method for securing satisfactory information on this point. Some impression may be secured from the differences in the intensity of the four actions which were used to compare the results of oral and parenteral courses.

In the patient with the persistent ectopic auricular tachycardia (Fig. 4A) the parenteral route supplied so much more action on the heart as to convert a therapeutic failure into a therapeutic success. In routine therapy it would not have been practical to extend dosage beyond that causing vomiting. In each of three experimental trials by the oral route the patient became violently ill with gastrointestinal toxicity; and only when additional oral doses were given at this time, did enough action develop in the heart to alter the rhythm. Against this there was the experience with the parenteral doses in four trials, in each of which the cardiac rhythm was altered without gastrointestinal toxicity.

In the case of the change in the RT-T segments as a measure of action (Figs. 2A, 8A to 10A and 12A to 15A) we averaged the change in terms of the arbitrary units combining lead I and lead II (eight digitalizations). For the most severe test of the thesis, the average value at the time gastrointestinal toxicity started in the oral courses was compared with the average value *prior to the dose* which resulted in gastrointestinal toxicity in the parenteral courses. The value for the oral ones was 3.4 units and for the parenteral ones 6.0 units. We have no way of knowing how much digitalis action on the heart this difference represents. These results show that at the level of cardiac action at which the oral courses caused vomiting almost three clearly distinguishable grades of digitalis action on the heart could be added without producing vomiting when the drug was given by the parenteral route.

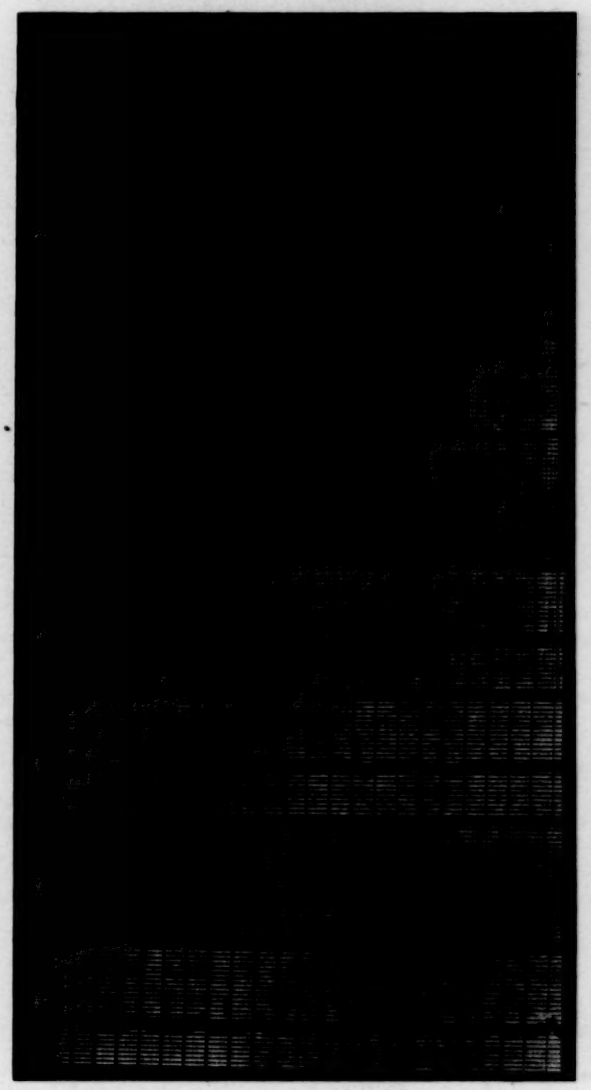


FIG. 4. B, tracings showing the types of rhythm changes in the experiment of Figure 4A. Auricular ectopic tachycardia (tracings 1 and 2) converted to auricular fibrillation (tracing 5) or sinus rhythm (tracing 8) by digitoxin.

In the case of the six digitalizations in which prolongation of A-V conduction was a measure of cardiac action there are three (Figs. 8, 10 and 14) in which the differences were small although unequivocal. In the remaining three the differences were quite pronounced: In one (Fig. 13) the oral course at the threshold of vomiting produced no change in the P-R interval of 0.16, while the parenteral route increased the P-R interval to 0.20 without vomiting; in another

(Fig. 12A) the oral course produced an equivocal change in the P-R interval (from 0.19 to 0.20) at the threshold of vomiting, while the parenteral course prolonged the P-R interval from 0.20 to 0.26 without vomiting; in the third case resulted in vomiting; in the other case (Fig. 6) gastrointestinal toxicity appeared when the rate had declined to 151 in the oral course while in the parenteral course the rate was down to 77 prior to the dose which resulted in vomiting.

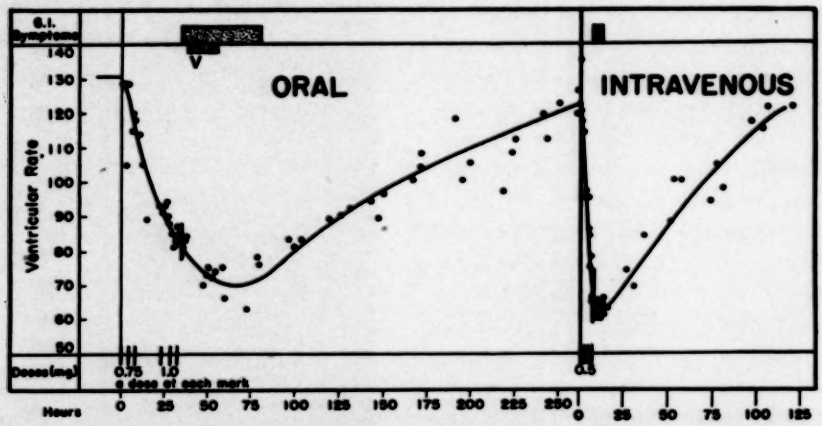


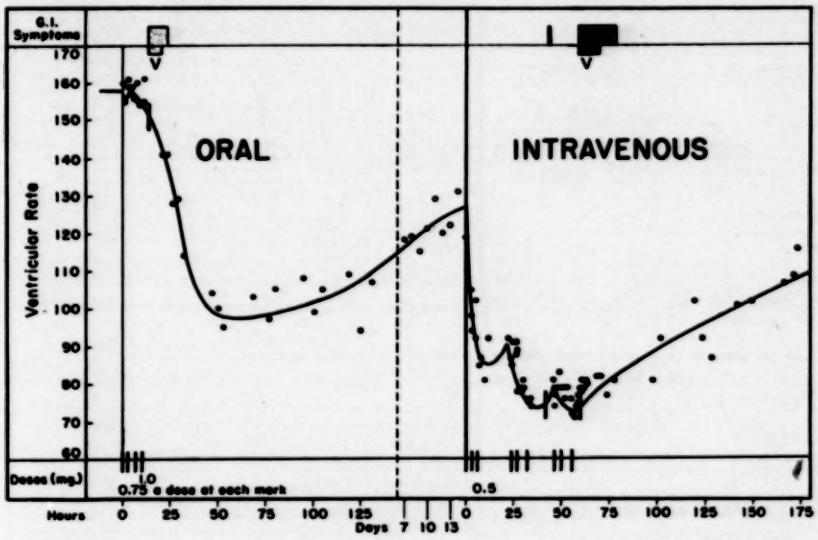
FIG. 5. Digoxin; cardiac action measured by slowing of heart rate in auricular fibrillation. The oral course was given during a period of thirty-two hours, a total of 5.25 mg. in six doses. The amount which reduced the rate to 82 caused gastrointestinal toxicity, beginning 2.3 hours after the last dose, lasting 46 hours with vomiting during a period of 19 hours. After an interval of 10 days an intravenous course was given during a period of 6 hours, 4 doses of 0.5 mg. each. When the cardiac action in this course reached a similar level (reduced rate to 82), there was no gastrointestinal toxicity. Even considerably greater cardiac action (rate reduced to 60) was attended by only brief nausea without vomiting (appeared one hour after last dose and persisted six hours).

(Fig. 15A) both routes of administration caused fairly marked P-R changes, but in the oral course the P-R interval rose from 0.20 to 0.26 at the threshold of vomiting while in the parenteral course the P-R interval rose to 0.29 with dropped ventricular beats (Fig. 15B) without vomiting.

The slowing of the heart rate in patients with auricular fibrillation as a measure of action presents a special problem because of the fact that below a particular rate considerably more digitalis action on the heart may be produced with little or no further change in the rate.[8] In all five experiments with auricular fibrillation the rate to which the heart beat declined at the level of onset of gastrointestinal toxicity in the oral courses was reproduced in the parenteral courses without vomiting. The additional slowing in the parenteral courses *before* the dose that resulted in vomiting was fairly small in three cases (Figs. 3, 5 and 7) but quite large in two others; in one (Fig. 11) gastrointestinal toxicity appeared when the rate had declined to 68 in the oral course while in the parenteral course the rate was down to 53 prior to the dose which

COMMENTS

Greater Cardiac Action without Emetic Action by Parenteral Than by Oral Doses. The results show that digitalis glycosides in sufficient dosage give rise to gastrointestinal toxicity whether the drug is administered by the oral or parenteral route. This is well known. However, they further show —and this not well known—that when the gastrointestinal tract is by-passed through parenteral administration more action on the heart may be produced without gastrointestinal toxicity than is possible through the oral route with doses up to the threshold of vomiting. How much more cardiac action is possible by the parenteral route has not been determined, but there is evidence that the difference may be of practical importance. The phenomenon applied to all of the nine patients in whom digitalization was carried out by a slow cumulative system. It failed to manifest itself in one case in which the digitalization was too rapid. (Fig. 9A.) It applied to all the digitalis materials tested (three different glycosides of the digitalis series, digitoxin, digoxin and lanatoside C; and to the



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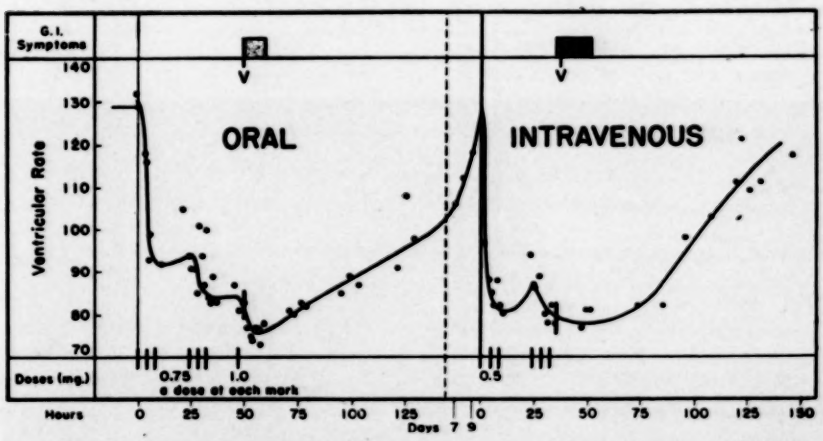

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FIGS. 6 and 7. Digoxin; the experiment of Figure 6 was repeated eleven days later (Fig. 7) in the same patient with auricular fibrillation. The two experiments show the same qualitative relationship between the effects of the oral and intravenous courses: In Figure 6 the oral course produced vomiting lasting 7 hours at a time when the cardiac action was very small (reduction of rate from 160 to 151); 14 days later the intravenous course produced a much greater cardiac action, reducing the heart rate to 78 before the dose which caused vomiting. The ratio of the cardiac to the emetic action by the intravenous route appears, therefore, much greater than that by the oral route, a larger difference than in any of the other experiments. It is probable, however, that the actual difference between the oral and intravenous routes is not nearly so great, the difference being accentuated by the fact that failure was more advanced at the time of experiment 6 and the fact that the oral course was given rapidly (4 doses in a period of 10 hours), whereas the intravenous course was given much more slowly (8 doses in 51 hours, prior to the dose which induced vomiting). The rapid oral course would be expected to produce a "local emetic" action early in much the same way as a massive single oral dose acts. To compare the ratio of cardiac to emetic activities by the oral and intravenous route the effect of massive doses is avoided by digitalizing slowly. This was done in the experiment of Figure 7 in which the oral course involved 7 doses given during a period of 48 hours. In this case, when vomiting began, the corresponding action on the heart was represented by slowing of the rate to 82. The same action on the heart (slowing to 82) was now reproduced by the slow intravenous digitalization but without vomiting (after the third dose shown in the figure). Two additional intravenous doses given in the ensuing 20 hours showed negligible further slowing (rate 79), and still without gastrointestinal toxicity. Only after another dose (6 doses in all during a total period of 32 hours) was the level of digoxin action sufficient to cause vomiting by the intravenous route. Figure 7, therefore, shows that a level of cardiac action brought on by the oral route was reproduced by the intravenous route, but in the oral course with vomiting and in the intravenous course without vomiting. It further shows that the intravenous course required approximate doubling of that dosage before the threshold of "systemic" vomiting was reached.

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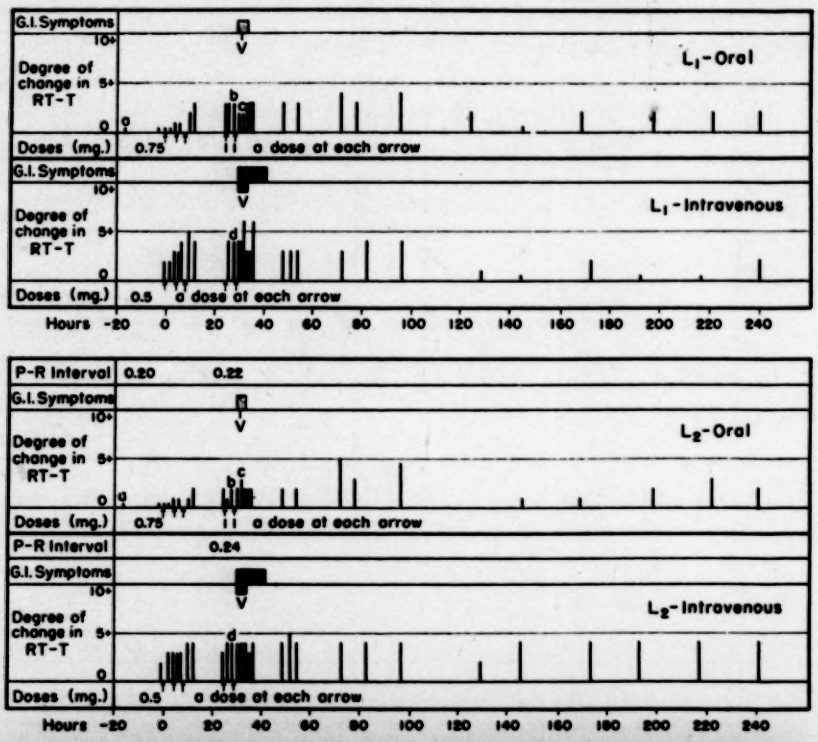

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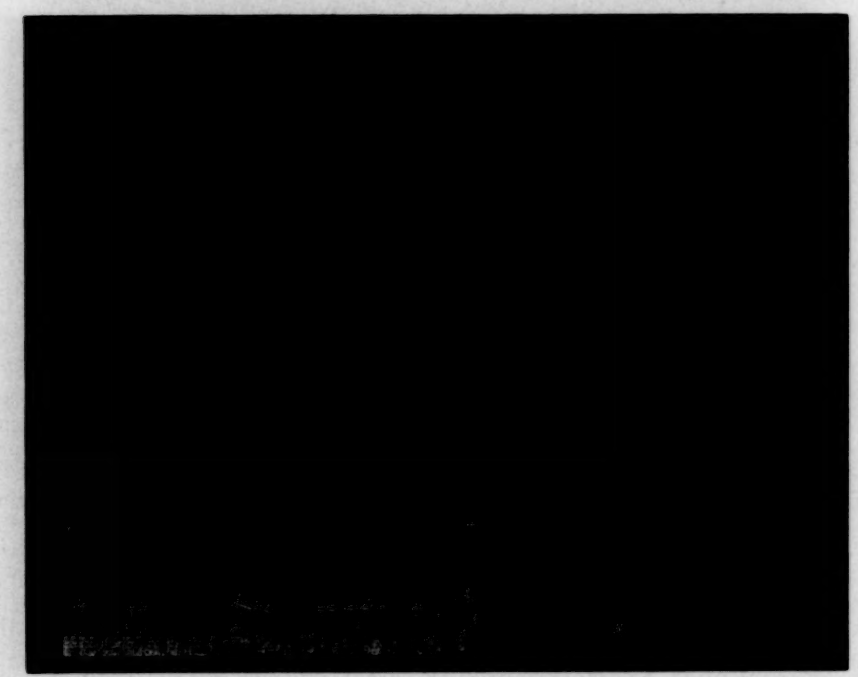
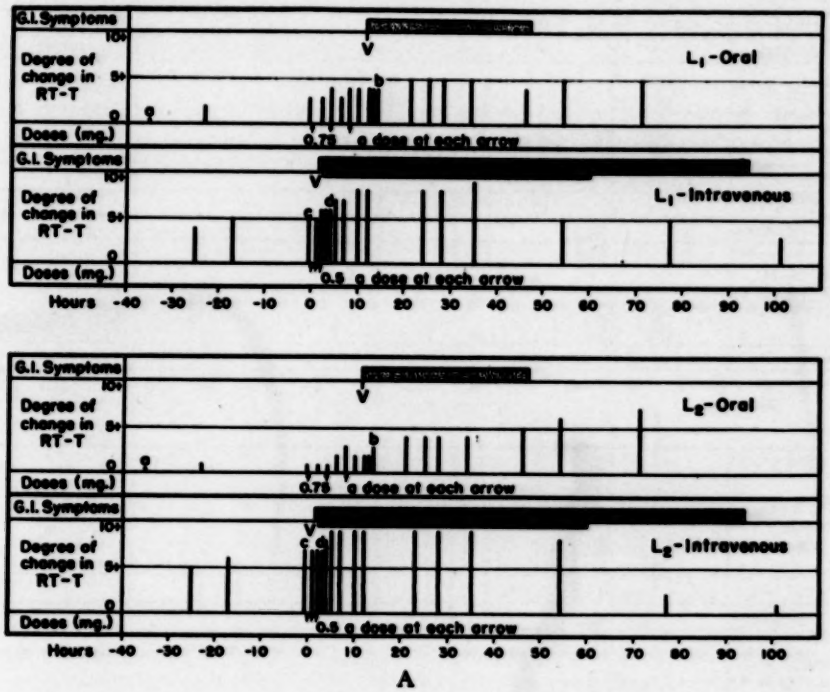
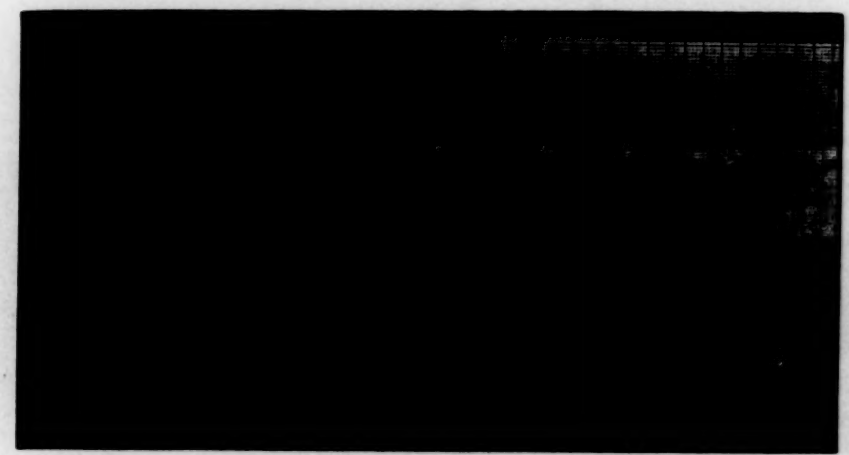


FIG. 8. A, digoxin; cardiac action measured by changes in RT-T and in P-R intervals. The oral course was given during a period of 28 hours, a total of 4.25 mg. in 5 doses. Gastrointestinal toxicity appeared 1.5 hours after the last dose. It persisted 4 hours, with vomiting once. After an interval of 10 days the intravenous course was given during a period of 28 hours, a total of 2.5 mg. in 5 doses. It also produced gastrointestinal toxicity which began 2 hours after the final dose and lasted 11 hours, with vomiting during a period of 3 hours. Note, however, the much greater cardiac action before emesis in the intravenous course, as shown by the RT-T changes and longer P-R intervals. B, sample tracings of RT-T and P-R changes from experiment of Figure 8A. Note that in the intravenous course (*d*) the cardiac effects without gastrointestinal toxicity are greater than in those in the oral course to the point of vomiting (*c*). * Tracing corresponds to (*b*) in a repetition of the oral course; both represent the greatest cardiac action before the dose which caused vomiting by the oral route and, although they are not identical, both show less cardiac action than (*d*), the greatest cardiac action without vomiting in the intravenous course.

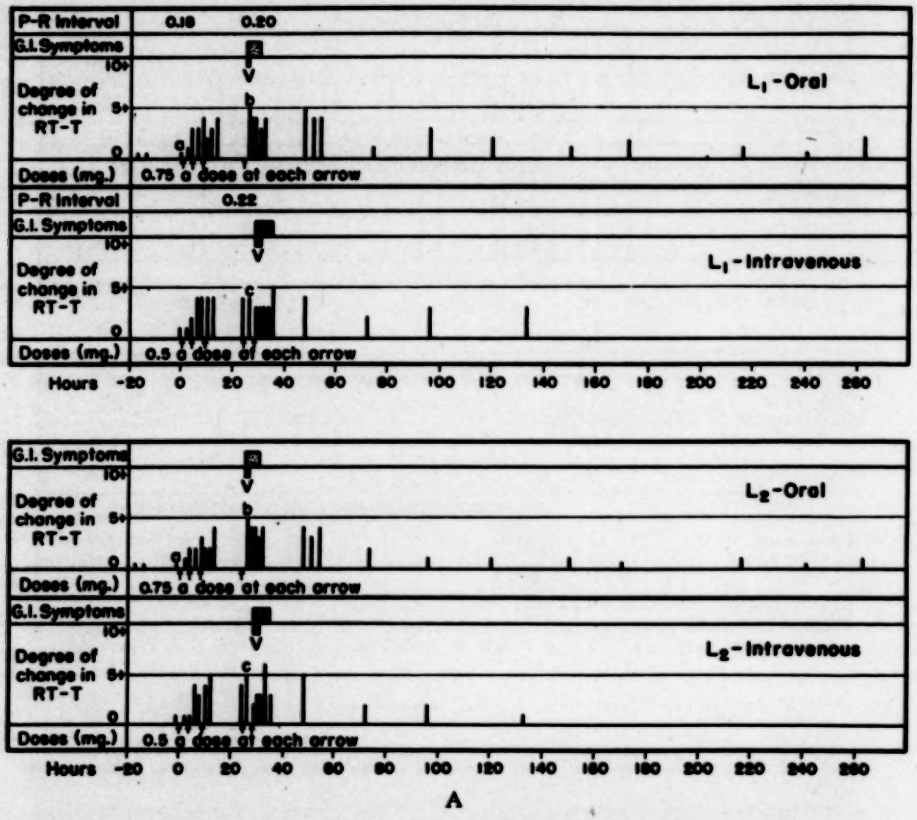

G.I. Symptoms
Degree of change in RT-T
Doses (mg.)
L_1-Oral
0.75 g dose at each arrow
L_1-Intravenous
0.5 g dose at each arrow
L_2-Oral
0.75 g dose at each arrow
L_2-Intravenous
0.5 g dose at each arrow
Hours -40 -30 -20 -10 0 10 20 30 40 50 60 70 80 90 100

A



B

FIG. 9. A, digoxin; cardiac action measured by changes in RT-T. The oral course was given during a period of 8 hours, 3 doses of 0.75 mg. each. Gastrointestinal toxicity appeared 1.5 hours after the final dose and lasted 35 hours, with vomiting once. After an interval of 3 days, before there was appreciable falling off of the cardiac action, the intravenous course was given during a period of two hours, 3 doses of 0.5 mg. each. It also produced gastrointestinal toxicity (anorexia, nausea), which began 0.5 hour after the second dose and lasted 94 hours, with vomiting during a period of 57 hours. Unlike all others, no appreciable increase in cardiac action without emesis occurred with the intravenous course. This may be due to the excessively rapid repetition of doses. The case presented other unusual features: unduly long persistence of digoxin action; greater cardiac action present before the first intravenous dose than at the time vomiting began in the oral course. B, sample tracings of RT-T changes from experiment of Figure 9A. This is an unusual case. Note that the cardiac action as shown by changes in the RT-T at the onset of gastrointestinal toxicity in the oral course (*b*) was less than that three days later before the first intravenous dose (*c*).



A

B

FIG. 10. A, digoxin; cardiac action measured by changes in the RT-T and in P-R intervals. The oral course was given during a period of 24 hours, 4 doses of 0.75 mg. each. Gastrointestinal toxicity appeared 1 hour after the final dose and persisted 5 hours, with vomiting for 0.5 hour. After an interval of 11 days the intravenous course was given during a period of 28 hours, 5 doses of 0.5 mg. each. It also produced gastrointestinal toxicity which began 0.5 hour after the final dose and lasted 6.5 hours, with vomiting for 1.5 hours. In this case the difference in the relation of the cardiac to the emetic action in the oral and intravenous courses is small but distinct. It is best shown in lead II. The evidence in the RT-T change is supplemented by the longer P-R interval. B, sample tracings of RT-T and P-R changes from experiment of Figure 10A. While the differences are not marked, lead II shows RT-T changes in the oral course at the point of vomiting (*b*) that are similar to those prior to the emetic dose in the intravenous course (*c*). The greater cardiac action before the emetic dose in the intravenous course is also shown by the longer P-R interval at (*c*).

purified mixture of glycosides, digifoline). It was not confined to any special manifestation of digitalis action on the heart, for the results were similar whether the action on the heart was measured by the RT-T changes of the electrocardiogram, the effect on A-V conduction (P-R intervals of the electrocardiogram), slowing of the heart rate in auricular fibrillation or the property of digitalis by which it suspends an ectopic tachycardia and restores the normal rhythm. These experiments have embraced a fairly wide range, if not all, of the more significant actions of digitalis on the heart. The action on systolic force[7] was not tested directly but there is indication that this action is involved in the vagal slowing of the ventricle in patients with auricular fibrillation.[8] Without exception there was in evidence this observation, namely, when the drug was given by the parenteral route a degree of cardiac action was attained without vomiting, which was not possible without vomiting when the drug was given by the oral route.

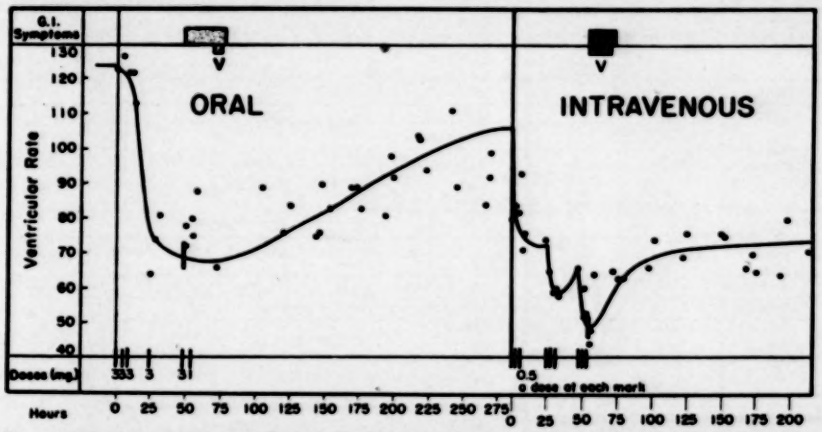


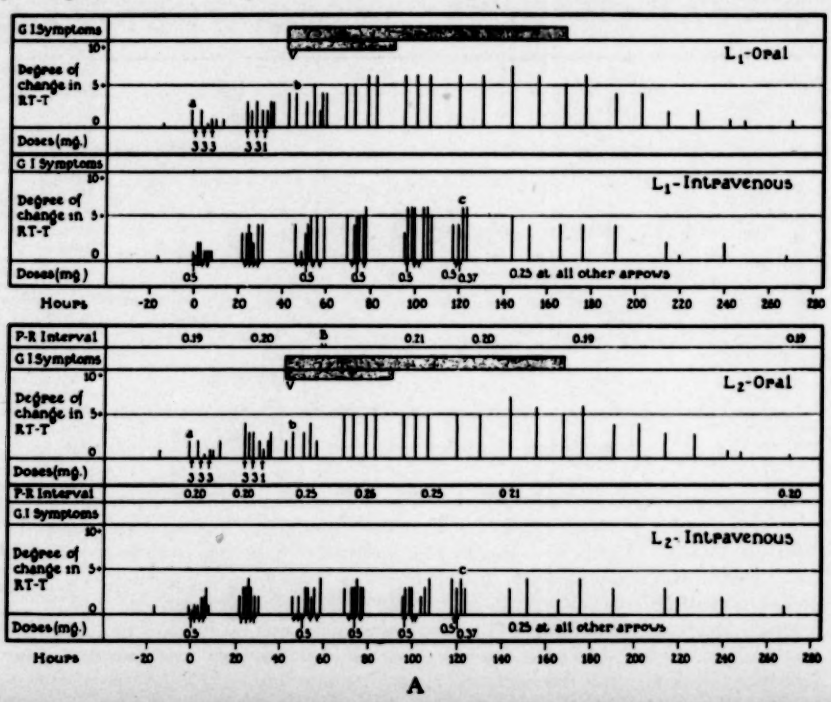
FIG. 11. Lanatoside C (cedilanid). Cardiac action measured by slowing of heart rate in auricular fibrillation. The oral course was given during a period of 54 hours, a total of 16 mg. in 6 doses. The amount which reduced the rate to 68 caused gastrointestinal toxicity, lasting 28 hours, with vomiting for 6 hours. After an interval of 10 days the intravenous course was given during a period of 53 hours, 9 doses of 0.5 mg. each. Note that now there was no toxicity when an approximately similar degree of cardiac action had developed, rate reduced to 68 (after fourth dose), and that only after 5 additional doses which lowered the rate to 48 was gastrointestinal toxicity induced by the intravenous course.

Parenteral Doses to Supplement Oral Digitalization in Special Cases. There is precedent for such practice. Ray and LaDue[9] gave fairly large doses of lanatoside C intravenously with advantage to patients who were under the effects of considerable amounts of oral digitalis; but since their study had a different purpose, their observations do not bear directly on our results.

Oral digitalization has been generally advocated, especially in this country, as the method of choice for securing all the therapeutic effects of digitalis. We have shared that position. It now seems that this point of view may have restricted the therapeutic potentialities of the drug: With the oral route, gastrointestinal toxicity may have led to the interruption of treatment prior to full cardiac action; cardiac action might have been carried further along had the drug been given by a parenteral route. As matters stand, it would seem far from wise to turn to the parenteral route for routine digitalization, although there are here indications that small parenteral doses might be used with advantage to intensify the cardiac actions in some cases in which one finds it necessary to interrupt an oral course of digitalization before the therapeutic results are sufficient, because of gastrointestinal toxicity. This would not simplify the technic of digitalization. It would make it more difficult, for vomiting is an unmistakable sign, but the fact remains that the results of these experiments indicate that beyond the point of vomiting after oral digitalization one may secure more action on the heart with parenteral doses without emetic action. In the event that small parenteral doses are given, the appearance of premature contractions or vomiting (systemic) may serve as warning signs. Experience should help determine what signs may be most safely depended

upon in such cases to indicate the limits beyond which the action of digitalis may not be carried with safety.

Site of Gastrointestinal Toxicity in Conventional Oral Methods of Digitalization. Up to about forty years ago it was the prevailing view that vomiting after members of the digitalis group was caused by local "irritation" of the gastrointestinal tract. The studies of Hatcher and his collaborators[10,11] were chiefly instrumental in drawing attention away from this point of view. They demonstrated that members of the digitalis group in doses within the therapeutic range caused vomiting by a "systemic" action (vomiting after intravenous doses in the eviscerated animal), and further, that the site is not the vomiting center in the medulla. The experiments of Koppanyi in 1930[12] also pointed in the same direction, and the more recent experiments of Borison and Wang[13] led them to the con-



A

B

FIG. 12. A, lanatoside C (cedilanid); cardiac action measured by changes in RT-T and in P-R intervals. The oral course was given during a period of 32 hours, a total of 16 mg. in 6 doses. Gastrointestinal toxicity appeared 11 hours after the final dose and lasted 127 hours, with vomiting during a period of 48 hours. After an interval of 12 days the intravenous course was given during a period of 120 hours, a total of 6.62 mg. in 21 doses. Note that the RT-T changes were greater and the P-R intervals were longer in the intravenous course which failed to produce any gastrointestinal toxicity. B, sample tracings of RT-T and P-R changes from experiment of Figure 12A. Note that the cardiac actions at the point of vomiting in the oral course (*b*) are far less than those during the intravenous course (*c*) in the absence of gastrointestinal toxicity.

clusion that vomiting after intravenous doses of digitalis glycosides is not due to an action on the vomiting center but to an action on a superficial area in the region of the ala cinerea, which they defined as the "central chemoreceptor trigger zone," distinct from the vomiting center.

The work of Hatcher exerted a strong influence. It was not long before clinical inferences appeared in the literature which seemed reasonable but for which proof was wanting. The assumption was made that the mechanism responsible for vomiting from intravenous doses was the same as that from oral doses. There also developed the view which is almost universally held at the present time that when digitalis is given in relatively small oral doses, for example, 0.3 gm. every four to six hours, the vomiting which may result in the course of time is an action brought about by systemic cumulation. The result is ascribed to a systemic action by reason of the fact that the repeated doses are small, that other systemic actions are in evidence (electrocardiographic actions, slowing of the rate in auricular fibrillation, heart block, premature contractions, etc.) and that many hours have elapsed after the first dose before the vomiting occurs. All of these are suggestive but none is proof that the vomiting is a systemic action. Time is often used as a deciding factor for distinguishing a "systemic" from a "local" emetic action. When an oral dose causes vomiting within a few minutes to an hour or two, it is considered an action on the gastrointestinal tract;[2] but if many hours elapse, it is considered a "systemic" action from the drug that has been absorbed.

In the recent study on cats to which we have referred there were some observations which were unexpected and surprising. The animals received oral doses of various digitalis glycosides, and in a large proportion of them vomiting occurred for the first time ten hours or longer after the oral dose. In these cases we anticipated a great deal of systemic action but we were surprised to discover that many of these animals, when tested by the method of titration, showed no evidence of systemic digitalis action. Here then were animals which vomited for the first time ten hours or longer after an oral dose of a digitalis glycoside from an action on the gastrointestinal tract. It seemed no longer safe to exclude an action on the gastrointestinal tract when vomiting in man occurs ten hours or longer after the beginning of oral doses. The following formulation seemed reasonable: Digitalis and its glycosides exert a local emetic action in the gastrointestinal tract; not all of the drug is absorbed; even the part absorbed may produce a subthreshold degree of this action; it may increase in intensity as additional doses are given; and these may summate until the threshold of emetic activity is reached.

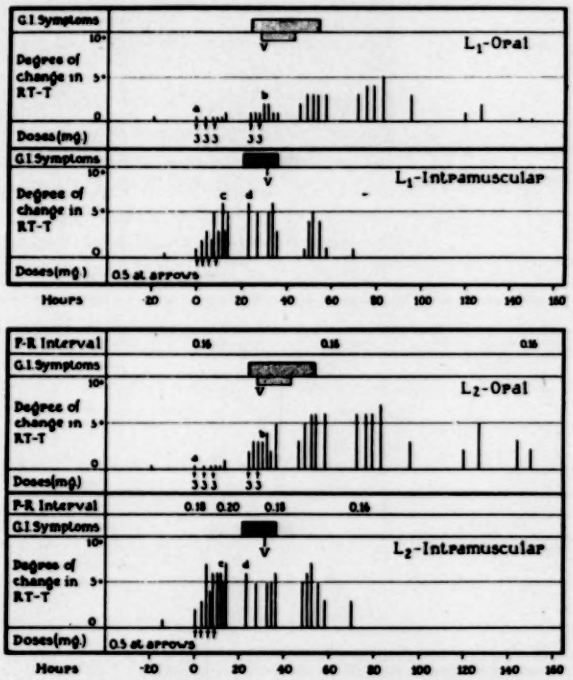


FIG. 13. A, lanatoside C (cedilanid); cardiac action measured by changes in RT-T and in P-R intervals. The oral course was given during a period of 28 hours, 5 doses of 3 mg. each. Anorexia and nausea appeared after the third dose and lasted 30 hours, with vomiting during a period of 15 hours. After an interval of ten days the intramuscular course was given during a period of 9 hours, 4 doses of 0.5 mg. each. It also produced gastrointestinal toxicity which began 12 hours after the final dose and lasted 15 hours, with vomiting once. Note the greater cardiac action in relation to the emetic action during the intramuscular course.

An important practical point is involved. When several oral doses of digitalis are given at intervals and vomiting occurs several hours after the onset of therapy, the patient is considered "overdigitalized," or at least, that there is as much digitalis action on the heart as is desirable and that the drug should be discontinued at this point. If, on the other hand, the vomiting results from the slow evolution of an action on the gastrointestinal tract, it may not only represent a protection against cardiac poisoning but also a bar against the full therapeutic action on the

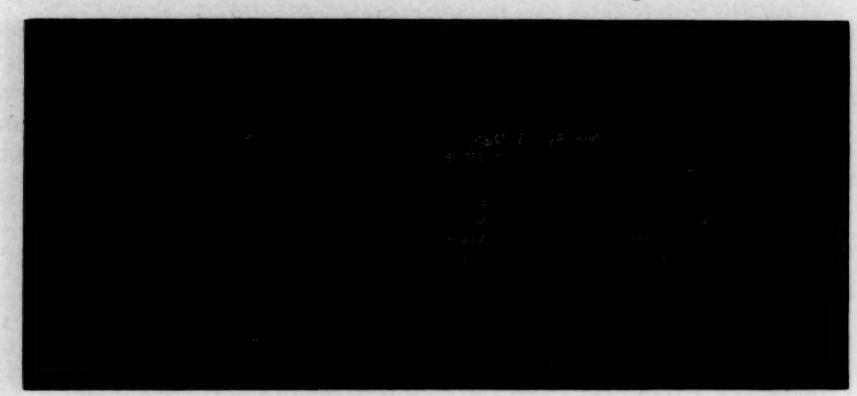


FIG. 13. B, sample tracings of RT-T and P-R changes from experiment of Figure 13A. Note that the cardiac actions at the point of vomiting during the oral course (*b*) were much less than those during the intramuscular course (*c*) prior to the development of gastrointestinal toxicity.

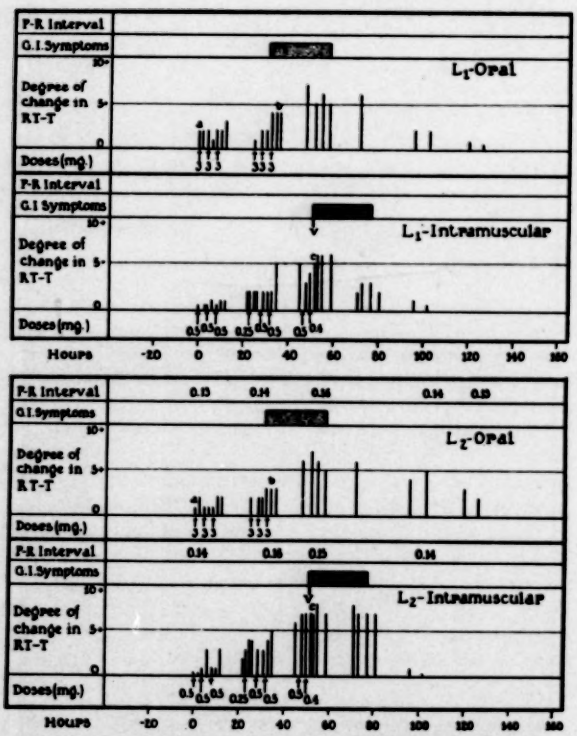


FIG. 14. A, lanatoside C (cedilanid); cardiac action measured by changes in RT-T and in P-R intervals. The oral course was given during a period of 32 hours, a total of 18 mg. in 6 doses. Gastrointestinal toxicity (abdominal cramps, diarrhea, nausea, no vomiting) appeared 2 hours after the fifth dose and persisted for 27 hours. After an interval of 5 days an intramuscular course was given during a period of 49 hours, a total of 3.65 mg. in 8 doses. It also produced gastrointestinal toxicity which began 2 hours after the final dose and persisted for 27 hours (nausea throughout and vomiting once). Note that during the intramuscular course at a point several doses prior to the level which caused vomiting, the cardiac actions were much greater than during the oral course at the point of gastrointestinal toxicity.

heart. The present results show that more cardiac action can be obtained without vomiting if the drug is given by parenteral injection. They indicate that the prevailing view may be erroneous, that vomiting which occurs several hours after oral doses may, at least in part, represent the accumulation of an emetic action in the gastrointestinal tract. This receives strong support from the animal experiments. It should be pointed out, however, that in regard to mechanism the evidence is not decisive. Intravenous doses give rise to peak concentrations of the drug in the blood stream such as are never reached by oral doses. These might alter the distribution of the drug and give rise to relatively greater cardiac than "systemic emetic" action and that the latter rather than a "local" action on the gastrointestinal tract may account for the results we have obtained. Additional experiments by the intramuscular route which does not produce the high peaks of concentration may provide more decisive proof.

It seemed possible that a difference in the pattern of the "local" and "systemic" emetic response would help reveal the site of emetic action in the oral digitalization. Accordingly, pertinent data have been assembled in Table II. An inspection of this table reveals no conspicuous differences between the emetic responses in the oral and parenteral courses. In both, with all three glycosides, there is a fairly long interval after the last dose before gastrointestinal toxicity occurs, between 1 and 3.5 hours in three-fourths of the patients by either route (oral 1 to 21 hours, average about 6 hours; intravenous 0.5 to 12 hours, average 3 hours). The same is true in the experiments with the same glycoside (digoxin):

FIG. 14. B, sample tracings of RT-T and P-R changes from experiment of Figure 14A. Note that during the intramuscular course at a point several doses prior to the level which caused vomiting (*c*) the cardiac actions were much greater than during the oral course at the point of gastrointestinal symptoms (*b*).

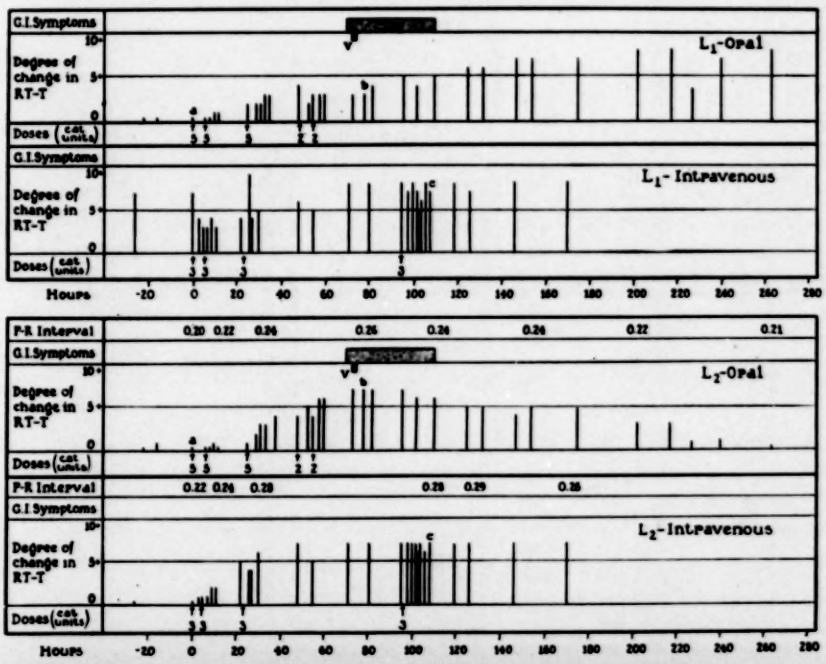


FIG. 15. A, digifoline; cardiac action measured by changes in RT-T and in P-R intervals. The oral course was given during a period of 55 hours, a total of 19 cat units in 5 doses. Gastrointestinal toxicity appeared 15 hours after the final dose and lasted 40 hours, with vomiting twice. After an interval of 11 days, before the cardiac action had disappeared, the intravenous course was given during a period of 96 hours, a total of 12 cat units in 4 doses. This produced no gastrointestinal toxicity. B, sample tracings from experiment of Figure 15A. Note that the cardiac actions at the time of gastrointestinal toxicity during the oral course (*b*) were exceeded during the intravenous course (*c*) in the absence of gastrointestinal toxicity. Note also the second degree A-V block in lead II at (*c*).

TABLE II

COMPARISON OF PATTERN OF GASTROINTESTINAL TOXICITY IN ORAL AND PARENTERAL DIGITALIZATIONS

Patient	Route	Dose (mg.)		Period from Last Dose to Gastrointestinal Toxicity (hr.)	Duration of Gastrointestinal Toxicity (hr.)
		Total	Single		
			Digitoxin		
He.Mi.	Oral	4.0	0.4	21.0	26
	I.V.	4.0	0.4	7.0	24
Ro.Ad.	Oral	4.4	0.4	6.5	143
	I.V.	2.0	0.4	3.3	4
			Digoxin		
He.Mi.	Oral	4.25	0.75,1.0	1.5	4
	I.V.	2.5	0.5	2.0	11
	Oral	3.25	0.75,1.0	1.5	3
Ro.Ad.	Oral	5.25	0.75,1.0	2.3	46
	I.V.	2.0	0.5	1.0	6
Be.Ho.	Oral	2.25	0.75	3.5	35
	I.V.	1.5	0.5	0.5	94
Da.Le.	Oral	3.0	0.75	1.0	5
	I.V.	2.5	0.5	0.5	7
Ma.Do.	Oral	3.25	0.75,1.0	2.5	9
	I.V.	4.5	0.5	3.5	19
	Oral	5.5	0.75,1.0	1.0	10
	I.V.	3.0	0.5	2.0	17
			Lanatoside C		
He.Mi.	Oral	16.0	3.0,1.0	11.0	127
	I.V.	6.62	0.5,0.25,0.37	....	...
Be.Mc.	Oral	18.0	3.0	3.0	27
	I.M.	3.65	0.5,0.25,0.4	1.0	27
Ha.Lo.	Oral	15.0	3.0	14.0	30
	I.M.	20.0	0.5	12.0	15
Ma.Sm.	Oral	16.0	3.0,1.0	1.3	28
	I.V.	4.5	0.5	1.0	18
			Digifoline (cat units)		
Ma.Si.	Oral	19.0	5.0,2.0	15.0	40
	I.V.	12.0	3.0	....	...

oral 1 to 3.5 hours, average 1.9 hours; intravenous 0.5 to 3.5 hours, average 1.6 hours. The duration of the emetic response in the oral and parenteral courses also shows no material difference with the three compounds: oral 3 to 143 hours; parenteral 4 to 94 hours. No difference between the emetic pattern of the oral and parenteral courses was in evidence in the same individual who received all three glycosides (patient He. Mi.): latent period (digitoxin) oral 21 hours, intravenous 7 hours; (digoxin) oral 1.5 hours, intravenous 2 hours; (lanatoside C) oral 11 hours, intravenous—no emesis; duration of emetic action (digitoxin) oral 26 hours, intravenous 24 hours; (digoxin) oral 4 hours, intravenous 11 hours; (lanatoside C) oral 127 hours, intravenous—no emesis.

The data in Table II are especially noteworthy in regard to the matter of individual variations as a warning against the danger of inferences drawn from isolated observations: The duration of gastrointestinal toxicity varied from 4 to 143 hours in the case of digitoxin, from 3 to 94 hours in the case of digoxin and from 15 to 127 hours in the case of lanatoside C.

Differences between Preparations. Four materials were used in this study on man: digitoxin, digoxin, lanatoside C and digifoline. The object was to ascertain whether the more favorable relationship of the cardiac to emetic actions in the case of the parenteral route has general application to the digitalis glycosides rather than to compare one preparation with another in respect to this point. For the latter purpose a much larger number of experiments would need to be carried out, and in accordance with a somewhat different plan. As the experiments were carried out, the results with different compounds were not the same even when tested in the same person. In the case of patient He. Mi. who received all three glycosides digitoxin caused vomiting in both the oral and intravenous courses and only the RT-T showed the more favorable relationship in the intravenous course; digoxin also caused vomiting in both the oral and intravenous courses but both the RT-T and P-R interval disclosed the more favorable relationship; and in the case of lanatoside C three factors established the more favorable relationship of cardiac to emetic actions by the intravenous route, namely, the RT-T, the P-R interval, and the fact that while the oral course produced gastrointestinal toxicity lasting many hours the intravenous course produced greater cardiac effect without any gastrointestinal symptoms. These differences may be accidental or due to the differences in the plans of dosage. In the study on cats to which reference has already been made the "local emetic" activity showed as much as a tenfold difference between one compound and another. With respect to this point, it would be a matter of interest and importance to compare the materials in common use.

SUMMARY AND CONCLUSION

1. The present study was carried out in man. The need for it was suggested by the results of a previous study in cats which showed that the digitalis glycosides may take ten hours or longer to develop an emetic action in the gastrointestinal tract after an oral dose. This is contrary to the prevailing belief, in accordance with which such a long period would be taken to indicate that the vomiting is the result of a "systemic" action of drug that has been absorbed.

2. The results show that if the gastrointestinal tract is by-passed through use of the intravenous or intramuscular route more action on the heart is possible without gastrointestinal toxicity in man than when the drug is given by the conventional methods of digitalization by small oral doses during a period of twenty-four to forty-eight hours or longer to the point of vomiting.

3. The results of the present study do not justify replacing the oral by the parenteral route for routine digitalization, although they indicate the possibility that the use of the oral route alone may have curtailed the therapeutic potentialities of members of the digitalis series and that supplementing the oral with intravenous doses may in some cases enhance the therapeutic results.

4. The more favorable relationship of the cardiac to the emetic actions of digitalis in man when the drug is given by the parenteral route indicates that the emetic response commonly referred to as "systemic" in the conventional slow oral methods of digitalization may not be "systemic" but the result of an action in the gastrointestinal tract.

5. The need for comparing the digitalis glycosides in common use with respect to the favorable relationship of the cardiac to the emetic actions by the parenteral route is indicated. The results may provide another basis for choice of a digitalis preparation.

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The Intramuscular Use of Pronestyl (Procaine Amide)*

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Philadelphia, Pennsylvania

THE value of procaine[3–6,12,17,19,22] and procaine amide[1,3–11,13,15,16,18,20,21] in the treatment of cardiac arrhythmias has been established by many investigators. Procaine has several disadvantages: it is rapidly hydrolyzed in the body so that it is difficult to maintain a therapeutic level; it produces central nervous system stimulation in the unanesthetized individual; and it is not effective when given by the oral route. These shortcomings have been largely obviated by the use of pronestyl (procaine amide).[13,14] This preparation has been administered orally as well as intravenously. Unlike procaine, pronestyl is not affected by the procaine esterase of the body and consequently maintains an effective plasma concentration for relatively long periods. Following intravenous administration the plasma levels decline slowly, about 10 to 20 per cent per hour.[14] With oral administration peak plasma levels occur in about one hour after which they closely approximate those following intravenous administration. About 50 to 60 per cent of procaine amide is excreted unchanged in the urine.

Although pronestyl is quite effective intravenously, the oral method is considered to be the one of choice. Most of the untoward effects that have been observed have occurred following the intravenous administration and are particularly prone to occur in older patients and in subjects with heart damage.[1] They consist chiefly in the development of hypotension, electrocardiographic abnormalities and, rarely, fatalities. Hypotension is relatively common and occasionally may be quite marked resulting in attacks of coronary insufficiency and convulsive seizures. The electrocardiographic effects consist of prolongation of the Q-T segment, widening of the ventricular complexes, alteration in T waves and ventricular tachycardia. Of the seventy-eight patients treated with intravenous and oral pronestyl in a series previously reported from this hospital, there were fifteen episodes of toxicity, mostly of a minor grade.[1] In addition, there were four patients who were in extremis in whom the administration of pronestyl was followed by death within forty-five minutes following the administration of the drug intravenously. Similar toxic effects have been observed by Miller, Nathanson and Griffith,[16] and Kayden et al.[9] Untoward effects are infrequently observed following oral medication; when seen they are usually mild in character, although recently agranulocytosis following oral maintenance doses of pronestyl was reported by Inouye, Miller and Townsend.[7]

Because of the toxicity associated with intravenous administration, it seemed advisable to evaluate the effects of an intramuscular preparation for parenteral use. This, while slower acting than when given by the intravenous route, would be simpler of administration and might have the advantage of being less toxic. The purpose of this investigation was to determine the therapeutic dose, relative efficacy and serum levels of intramuscular preparations of pronestyl and to compare these data with those obtained by the use of the oral and intravenous routes.

METHOD OF STUDY

The following preparations of pronestyl were used for the intramuscular injection: pronestyl gluconate† which has a molecular weight of 431.47 and has a content of pronestyl base of 54.51 per cent, and pronestyl hydrochloride, the drug currently available for intravenous use,

† Pronestyl gluconate solution and pronestyl hydrochloride were supplied by E. R. Squibb & Sons, New York.

* From the Division of Cardiology, Philadelphia General Hospital, and the Robinette Foundation, University of Pennsylvania. This work was aided by a grant from the U. S. Public Health Service and E. R. Squibb and Sons.

which has a molecular weight of 271.79 and a content of pronestyl base of 86.55 per cent. Both of these compounds were given intramuscularly in our series and their administration was unaccompanied with local evidence of irritation or swelling at the injection site despite the fact that volumes up to 15 cc. were used. Because pronestyl hydrochloride has a greater content of pronestyl base per cc., it was used in most of these experiments.

TABLE 1

SINGLE DOSE

	Dose	No. of Patients
Normal Subjects		
Pronestyl gluconate.....	1.0 gm. (550 mg.)*	4
Pronestyl gluconate.....	1.5 gm. (825 mg.)	4
Pronestyl hydrochloride..	0.5 gm. (425 mg.)	4
Pronestyl hydrochloride..	1.0 gm. (850 mg.)	7
Congestive Heart Failure		
Pronestyl hydrochloride..	1.0 gm. (850 mg.)	3
Pronestyl hydrochloride..	0.5 gm. (425 mg.)	1
Congestive Heart Failure with Renal Insufficiency		
Pronestyl hydrochloride..	1.0 gm. (850 mg.)	7
Renal Insufficiency		
Pronestyl hydrochloride..	1.0 gm. (850 mg.)	2
Pronestyl hydrochloride..	0.5 mg. (425 mg.)	1

MULTIPLE DOSES

Normal Subjects		
Pronestyl hydrochloride..	0.5 gm. (425 mg.)	2
Pronestyl hydrochloride..	1.0 gm. (850 mg.)	3
Congestive Heart Failure		
Pronestyl hydrochloride..	1.0 gm. (850 mg.)	1

* Pronestyl base

Determination of Serum Levels. Pronestyl gluconate in doses of 1,000 and 1,500 mg. (10 and 15 cc.) and pronestyl hydrochloride in doses of 500 and 1,000 mg. (5 and 10 cc.) were used for intramuscular injection. The types of cases studied and the pronestyl doses used are tabulated in Table 1. Prior to injection a control blood pressure, serum level and electrocardiogram were taken in most cases. Serum levels were repeated at periods of five, fifteen and thirty minutes, one, two, four and six hours in the majority of cases. This schedule was modified in a few of the patients. Blood pressures were taken at five-minute intervals after the injection for at least thirty minutes. A second electrocardiogram was taken at from fifteen minutes to one hour after the injection. In six patients the effects of multiple intramuscular doses were observed. The drug was given at six-hour intervals for three doses after a control serum level was obtained, and additional serum levels obtained from ten to thirty minutes after the first injection and then six hours following each injection just prior to the administration of the subsequent doses. In one case only two injections were given six hours apart.

Treatment of Arrhythmias. Arrhythmias were treated in a manner similar to the method outlined previously, using similar control studies. Following the administration of pronestyl a continuous electrocardiogram was taken for a period up to fifteen minutes in some cases, and then periodically at intervals of several minutes for thirty minutes or until the arrhythmia was terminated. In the majority of patients treated, control pronestyl serum levels were taken and additional levels were taken shortly after conversion of the arrhythmia if such occurred.

Chemical Procedures. The serum levels of procaine amide in this study were determined by an adaptation of the method of Bratton and Marshall[2] for sulfonamides. This differs from the method used by Mark et al.[14] in the omission of the benzene extraction procedure. The purpose of the benzene extraction is to separate procaine amide from its possible metabolic break down products, i.e., para-aminobenzoic acid. In addition, extraction into the organic solvent precludes the possibility of interference from sulfonamide drugs, and in patients with uremia the measurement of retained products of metabolism having a similar structure. However, Mark et al. point out that procaine amide in contradistinction to procaine is a very stable compound. After incubation of pronestyl for nineteen hours in human plasma at a temperature of 37°c. 95 per cent of the pronestyl was recovered in an unchanged state. Since most of our blood levels were taken over a six-hour period, we believed that we could safely eliminate the benzene extraction. In an occasional patient with severe uremia we noted a high control level of 0.2 to 0.4 mg. per cent which could be eliminated by preliminary extraction with benzene as described in the article by Mark et al. Several samples in non-uremic patients were run by both methods and satisfactory checks were obtained. We have found a fairly good correlation between the values

obtained with the method described below and that of Mark et al. Recoveries of pronestyl incubated with blood yield similar results by both methods. It is our impression that except in instances of severe uremia or in cases in which the patient has received or is receiving sulfonamide medication, the following method is adequate:

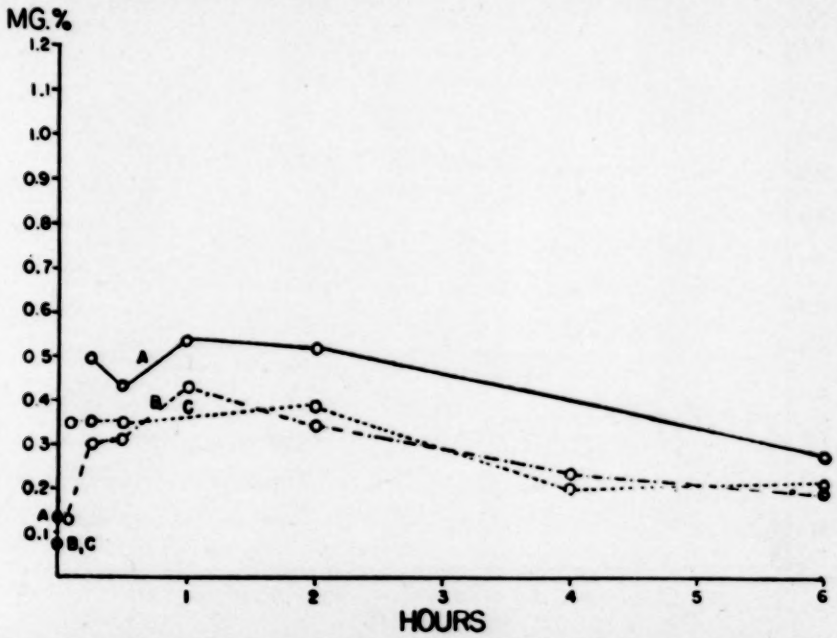

FIG. 1. Serum levels after 1.0 gm. of pronestyl gluconate (550 mg. pronestyl base) in normal subjects. (The time in hours following the intramuscular injection of pronestyl is plotted on the abscissa and the serum levels in mg. per cent of pronestyl hydrochloride are plotted on the ordinates. In Figures 1 to 6 each of three typical patients in one category are indicated by letters A, B and C. The control values for each patient are indicated on the ordinate by the corresponding letter and are not joined to the remainder of the graph for purposes of clarity. The circles represent serum levels taken at 5, 15 and 30 minutes and 1, 2, 4 and 6 hours after the injection in most of the graphs.) In Case A in this figure the first specimen following the injection was taken at ten minutes and the fifteen-minute specimen was eliminated; a four-hour specimen also was not obtained.

This method can be used with serum, plasma or whole blood. All specimens were run in duplicate. (1) Add 25 ml. of water to 1 to 3 ml. of biologic material in a volumetric flask. (If whole blood is used, allow it to stand for ten minutes). (2) Add 10 ml. of 15 per cent trichloracetic acid and dilute with distilled water to a total volume of 50 cc. Allow to stand for ten minutes. (3) Filter through a Whatman No. 42 filter paper. (4) Take a 10 ml. aliquot of the filtrate and place in an Evelyn cuvette. (5) Add 1 ml. of 0.1 per cent sodium nitrite, shake well and allow to stand for exactly three minutes. (6) Add 1 ml. of ammonium sulfamate, shake well and let stand for three minutes. (7) Add 1 ml. of the coupling reagent (N- (1-naphthyl) ethylene diamine dihydrochloride), shake well and let stand for ten minutes before reading.

Reagent blank: Prepare by diluting 10 ml. of 15 per cent trichloracetic acid to 50 ml., and treating a 10 ml. aliquot exactly as in steps 5, 6 and 7 of the aforementioned method.

Blood blank: Prepare by treating a 1 ml. sample of blood exactly like a regular blood sample with the exception that step 5 is omitted (add water, 1 cc. instead).

Standard: The pronestyl stock standard contains 0.1 mg. pronestyl hydrochloride per ml. Add 0.1 ml. of the pronestyl stock standard to 10 ml. of 15 per cent trichloracetic acid and dilute to 50 ml. with distilled water. A 10 ml. aliquot is then treated exactly as in steps 5, 6 and 7. The intensity of the color produced by the aforementioned reaction was measured in an Evelyn photoelectric colorimeter. The azo dye resulting from the coupling of diazotized pronestyl and N- (1-napthyl)-ethylene diamine

dihydrochloride has a peak absorption of light at a wave length of 545 μ as determined in the Beckman spectrophotometer, model DU., and obeys the Beer-Lambert law over the range of concentrations from 0.00 to 0.12 mg. pronestyl per ml. Higher concentrations were not checked.

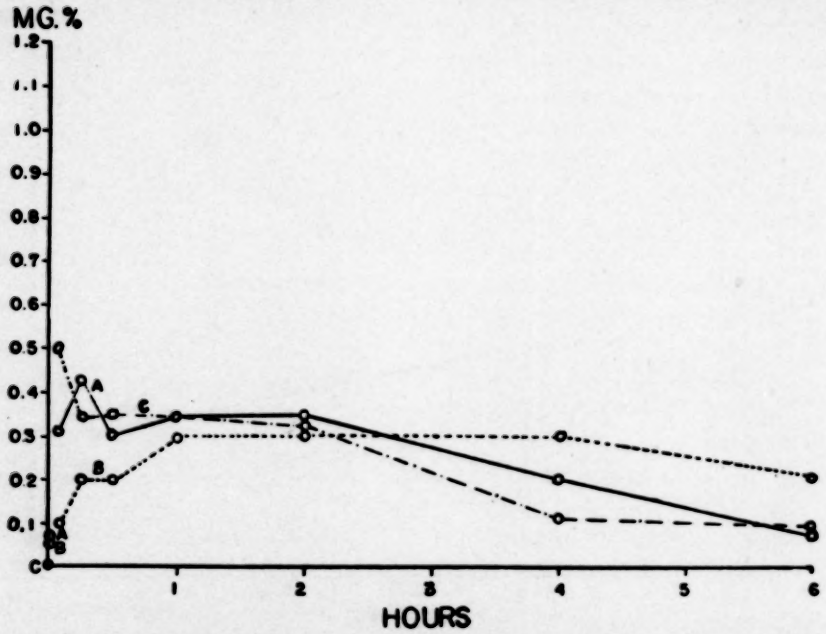

FIG. 2. Serum levels after 0.5 gm. of pronestyl hydrochloride (425 pronestyl base) in normal subjects.

Recoveries were also performed on whole blood *in vitro* and showed from 100 to 108 per cent recovery at a concentration of 0.02 mg. pronestyl per ml. blood. Recoveries were done on whole blood and plasma, and were equally satisfactory in both. Total pronestyl, as well as free pronestyl, was determined by hydrolysis with hydrochloric acid. No appreciable differences were observed.

RESULTS

Effect of Intramuscular Pronestyl on the Serum Level. The effect of the administration of pronestyl is shown in Figures 1 to 7. In each instance three of the more typical graphs were utilized to indicate these changes. Variations were noted in the serum levels after identical doses in different patients due possibly to variations in the patients' weight and differences in absorption and excretion. The figures for the serum levels of both pronestyl hydrochloride and gluconate are in terms of mg. of pronestyl hydrochloride per 100 cc. since pronestyl hydrochloride was used in the standard.

A. Effect of pronestyl gluconate, 1 gm., in subjects with normal renal function (Fig. 1): Note that the serum levels rise rapidly in the period of five to thirty minutes after injection and attain their maximum value within one hour after injection, after which they slowly decline; but even at the six-hour period at which time the levels are 0.18 to 0.28 mg. per cent they have as yet not fallen to the control level.

B. Effect of pronestyl hydrochloride, 0.5 gm., in patients with normal renal function (Fig. 2): The control levels range from 0.00 to 0.07 mg. per cent. Note that the general configuration of the curves is somewhat similar to that observed in Figure 1. The chief exception is that in two of the cases the maximum level is obtained in five and fifteen minutes, respectively, and the general plateau of concentration between one and four hours is slightly below that obtained in Figure 1, probably because the total amount of pronestyl base administered was less than in group A.

C. Effect of pronestyl gluconate, 1.5 gm., in patients with normal renal function (Fig. 3): The control levels range from 0.00 to 0.16 mg. per cent. Note the rise in serum concentration at five, fifteen and thirty minutes. The maximum concentration is attained in one hour, after which there is a gradual decline; however, even after five and one-half to six hours appreciable serum levels are present.

D. Effect of pronestyl hydrochloride, 1.0 gm., in patients with normal renal function (Fig. 4): The control values range from 0.01 to 0.10 mg. per cent. Note that the curves are somewhat similar to those observed in Figure 3. The content of pronestyl base is approximately the same in both series. Certain differences are observed as compared to Figure 3, namely, the maximum serum levels in A and B are obtained at the thirty-minute period and the decline in concentration is more rapid thereafter. Note that the serum levels at the end of six hours are still appreciable, as in Figure 3.

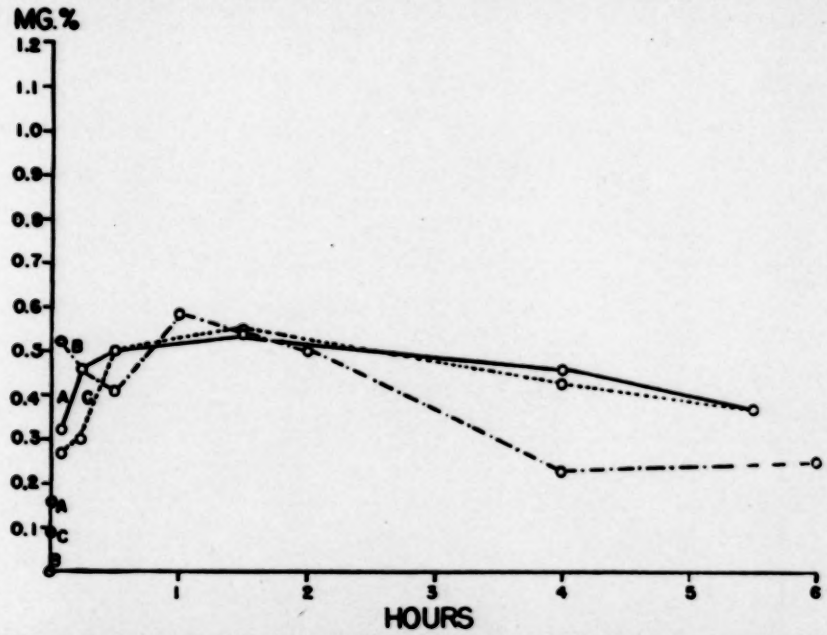

FIG. 3. Serum levels after 1.5 gm. of pronestyl gluconate (825 mg. pronestyl base) in normal subjects. In Cases A and C a one and one-half-hour sample replaced the one- and two-hour specimens and a five and one-half-hour specimen was obtained instead of a six-hour sample.

E. Effect of pronestyl hydrochloride, 1.0 gm., in congestive failure (Fig. 5): Note that the graphs are quite different from those shown in Figures 3 and 4 although almost identical quantities of pronestyl base were given. The chief differences observed are the higher levels obtained at five, fifteen and thirty minutes and the more gradual decrease in the serum level thereafter. At the end of six hours a rather high level is still present which ranges from 0.48 to 0.63 mg. per cent.

F. Effect of pronestyl hydrochloride, 1 gm., in patients with congestive heart failure and significant renal insufficiency (BUN 45 to 119 mg. per cent.) (Fig. 6): Note that the height of serum levels is similar to that observed in the group with congestive heart failure. (Fig. 5.) The decline of the serum levels is quite gradual and at the end of six hours a significant serum concentration ranging from 0.5 mg. per cent to 0.92 mg. per cent is still present. This point is of considerable importance in therapy and suggests that patients with heart failure, particularly with significant renal insufficiency, may require less of the drug, and that higher levels may be obtained than with similar doses used in patients with normal renal function. These levels may also be maintained for a longer period of time. This is not surprising since pronestyl is largely eliminated in the urine.

G. Effect of multiple doses: Intramuscular pronestyl hydrochloride was administered in multiple doses to six patients. Two patients with normal renal function were given three 1.0 gm. doses and two patients were given three 0.5 gm. doses at six-hour intervals; one patient with normal renal function was given two 1.0 gm. doses at six-hour intervals; and one patient with congestive heart failure and relatively mild renal insufficiency was given three 1.0 gm. doses at six-hour intervals.

The two patients who received 0.5 gm. doses of pronestyl hydrochloride manifested no cumulative effect. Three of the four patients who received 1.0 gm. doses, however, showed a definite cumulative rise in the serum levels.

One of these was the patient with congestive heart failure. Figure 7 represents the serum levels obtained in this patient. Note the peak effect ten minutes after the first injection, the high level present at the end of six hours and the progressive rise in the serum concentration in each of the two subsequent six-hour periods (twelve and eighteen hours, respectively).

Effect on Arrhythmias. The results of the treatment of twenty-nine episodes in twenty-four patients with various arrhythmias are summarized in Table II. They were quite similar to those reported following intravenous and oral medication. It should be noted that in some of the episodes, two arrhythmias were present simultaneously. In eight of the treated episodes

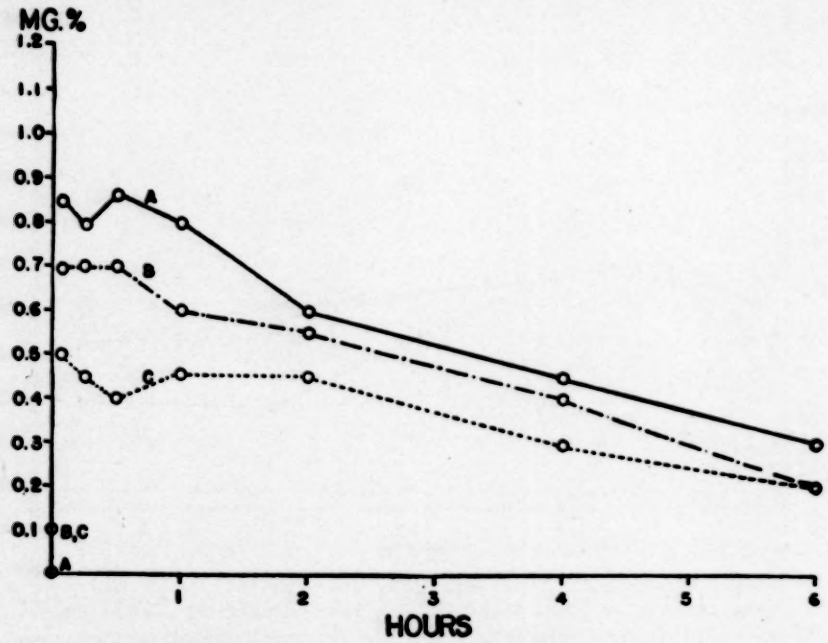

FIG. 4. Serum levels after 1.0 gm. of pronestyl hydrochloride (850 mg. pronestyl base) in normal subjects.

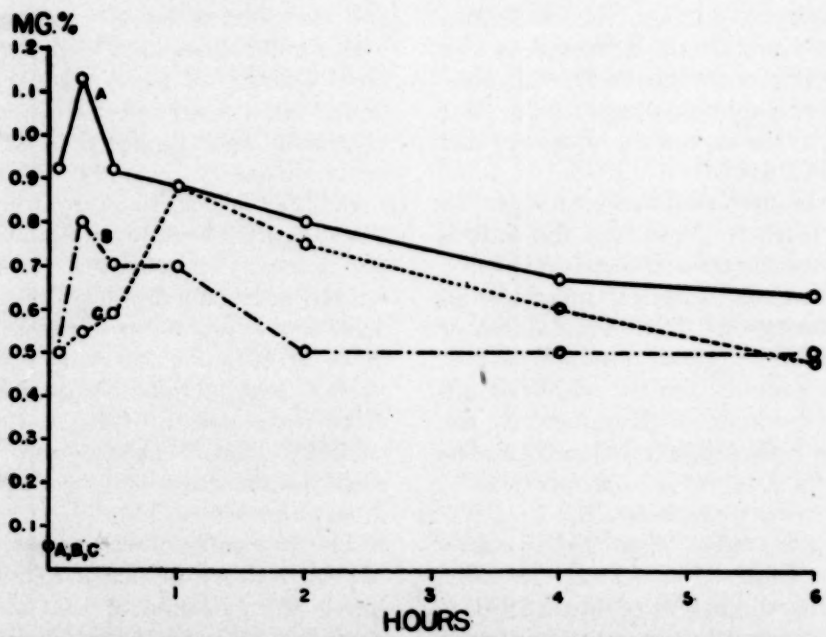

FIG. 5. Serum levels after 1.0 gm. of pronestyl hydrochloride (850 mg. pronestyl base) in patients with congestive failure and relatively mild renal insufficiency.

of ventricular premature contractions and two of the episodes of ventricular tachycardia, auricular fibrillation was also present. In one of the patients with paroxysmal auricular tachycardia, there were frequent ventricular premature contractions.

version occurred only after one hour and the change in rhythm may well have been coincidental rather than due to pronestyl. None of the eleven cases of auricular fibrillation were converted to normal rhythm in the doses given.

In the cases of this series a therapeutic effect,

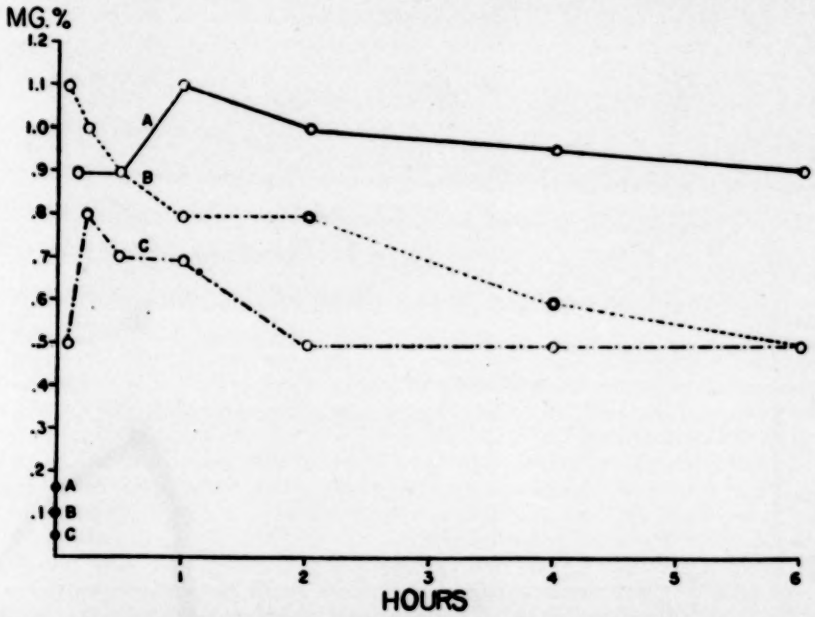

FIG. 6. Serum levels after 1.0 gm. of pronestyl hydrochloride (850 mg. pronestyl base) in patients with congestive failure and severe renal insufficiency. In Case A the first specimen following the injection was taken at ten minutes and the fifteen-minute specimen was eliminated.

Three episodes each of nodal tachycardia and ventricular tachycardia were abolished. In sixteen episodes characterized by ventricular premature contractions, thirteen demonstrated complete cessation or a significant reduction of the premature beats. In one subject the ventricular premature contractions became more frequent and a paroxysmal ventricular tachycardia developed. In one of the other two episodes which failed to respond, only 0.5 gm. of pronestyl hydrochloride was given and may have represented an ineffective dose. One case of bigeminal rhythm due to A-V nodal premature contractions was successfully treated. Only one of three cases of auricular flutter was converted to normal rhythm; two others continued with auricular flutter but manifested a reduction in the auricular rate. A fourth case of supraventricular tachycardia which probably represented auricular flutter was also converted to a normal sinus rhythm (Case 4). In two of three subjects auricular tachycardia was converted to normal sinus rhythm, although in one the re-

if it occurred at all, was almost always manifested within thirty minutes after the intramuscular injection of the drug, and frequently occurred within ten or fifteen minutes. This period coincides with the maximum serum levels.

Effect on Blood Pressure. Blood pressure studies before and after pronestyl therapy were made in eighteen patients. No significant change was observed in seven patients; a fall of blood pressure from 10 to 20 mm. systolic or both systolic and diastolic was noted in seven, and in four experiments a maximum drop of from 20 to 30 mm. was noted. This drop was transient in three patients and occurred in the period from five to thirty minutes after the administration of pronestyl and coincided with the peak serum levels. In none of these was clinical signs of hypotension observed; significant clinical evidences of hypotension after intravenous administration were reported in a previous article from this laboratory.[1] In twenty-six other patients in whom only occasional blood pressure

records were taken, there were no signs or symptoms suggestive of hypotension such as have been observed following the intravenous use of this drug.

It is our impression that although intramuscular pronestyl may result in a fall in blood pressure, it is less frequent and relatively slight as compared to that observed following intravenous medication.

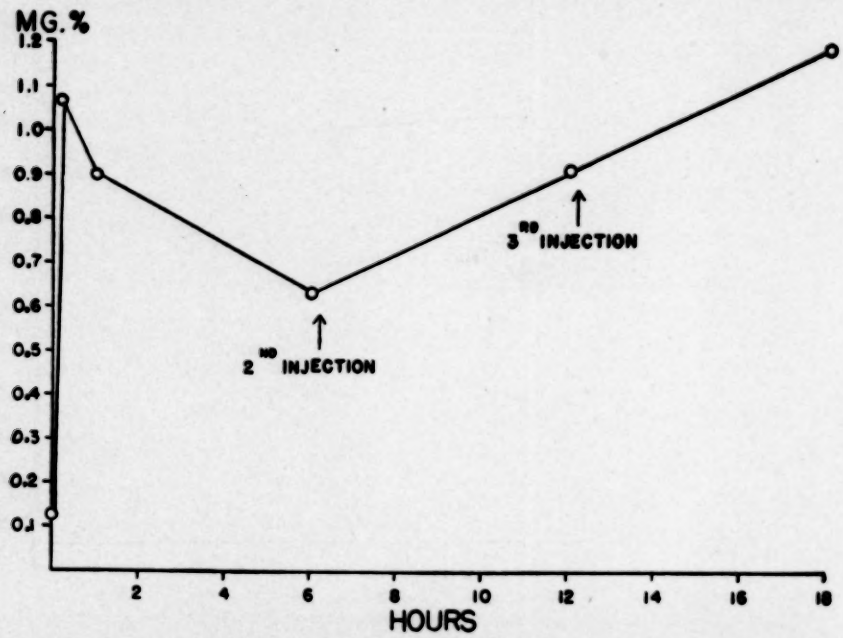

FIG. 7. Serum levels after 1.0 gm. of pronestyl hydrochloride (850 mg. pronestyl base) in a patient with congestive heart failure and moderate renal insufficiency given in 3 doses, each six hours apart.

Effect on the Electrocardiogram. The electrocardiographic changes following intramuscular injection were similar to those that have been described after administration by oral and intravenous routes. These consisted of lengthening of the Q-T interval, alteration in T waves and widening of the ventricular complexes in some patients.

Toxic Effects. Relatively few toxic effects were observed. In general the toxic effects were minimal and were not more marked than those which followed oral medication. We observed one transient episode of hysteria in an emotionally labile control subject. One patient complained of dizziness one hour after injection, but unfortunately a blood pressure reading was not obtained at this time. We did not observe any nausea or vomiting which could be ascribed to the drug. A patient with auricular tachycardia with a 2:1 A-V block developed a 1:1 response and a consequent rapid ventricular rate after the injection of 1 gm. of pronestyl hydrochloride (Case 29).

We observed a single serious toxic effect of pronestyl in this series. L. M. (Case 16), age twenty, with probable active rheumatic carditis, mitral stenosis and insufficiency, and auricular fibrillation was admitted with a moderate grade of heart failure. Digitoxin and thiomerin were administered for the heart failure. Because of frequent ectopic ventricular contractions accompanying the auricular fibrillation, 1 gm. of pronestyl hydrochloride was given intramuscularly on the morning after admission.

Electrocardiograms taken fifteen and thirty minutes after the injection of the pronestyl revealed more frequent ventricular ectopic beats which occurred in runs of two to eight in succession and constituted paroxysms of ventricular tachycardia. (Fig. 8.) These aberrant complexes resembled the ventricular ectopic beats observed before pronestyl was given but the width was considerably increased. Tracings taken at one, four and six hours showed a diminishing number of these complexes and a gradual return of the QRS interval to the duration observed in the control tracing.

The patient was found dead in bed forty-three hours after the single dose of pronestyl. Since

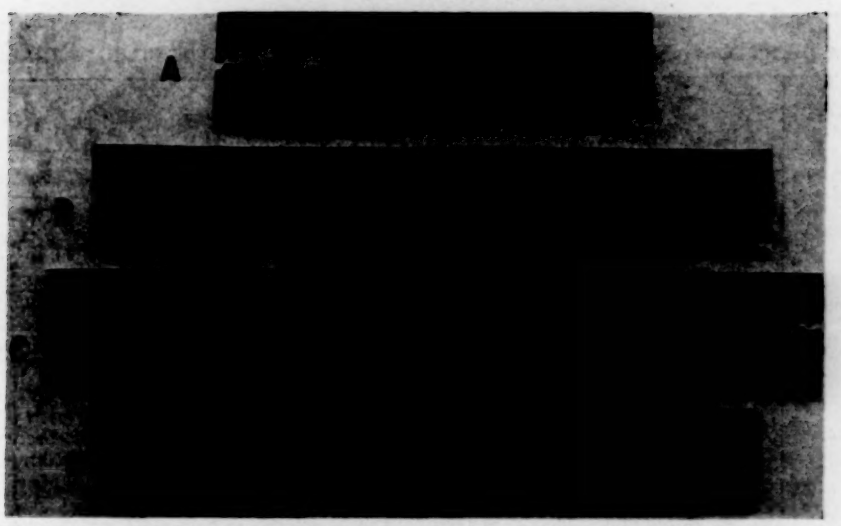

FIG. 8. Case 16. All tracings were taken on lead II. A, before the administration of pronestyl: the auricles are fibrillating and some aberration of the ventricular complexes is seen. The arrow points to a ventricular ectopic beat. B, fifteen minutes after the intramuscular injection of 1 gm. of pronestyl hydrochloride: the ventricular ectopic beats are more frequent and occur in runs constituting paroxysms of ventricular tachycardia. These ectopic beats are, for the most part, similar to the ectopic complex shown in A. An occasional ectopic beat originates from some other focus. There is marked widening of the QRS intervals of the ectopic beats compared to that in the control tracing, but not of the beats conducted from the auricles. C, thirty minutes after the injection of pronestyl: the tracing is similar to B. D, six hours after the injection of pronestyl: the ectopic beats are markedly reduced in frequency and not as widened; however, they are still more frequent and the QRS complexes wider than in the control tracing.

this patient appeared to be improved on the day following the administration of pronestyl at a time when the toxic pronestyl effects had disappeared, we believe that pronestyl was not the cause of death in this patient.

COMMENTS

Optimal Pronestyl Levels in Treating Arrhythmias. We are not certain as to the optimal serum level for the abolition of an ectopic rhythm. The figure apparently varies considerably and depends upon many factors. In most of our patients the effect upon the arrhythmia occurred at levels of 0.5 mg. per cent or higher, although in some the beneficial effect on the ectopic rhythm occurred after smaller doses of pronestyl and at lower serum levels. In the single dose method an effective level of plasma concentration, 0.5 mg. per cent, is attained in five to thirty minutes, and occasionally in one hour after the intramuscular administration of 1 gm of pronestyl hydrochloride. Since the serum level attained is slightly higher and the decline is slower in patients with congestive failure and renal insufficiency, relatively small doses may be sufficient when these conditions are present.

For the infrequent occasions when maintenance by the oral route is impractical, injection of 0.5 to 1.0 gm. of pronestyl hydrochloride intramuscularly at six-hour intervals should maintain an effective blood level. It is likely that in some patients a cumulative effect will occur with the larger dose. (Fig. 7.)

The Value of Intramuscularly Administered Pronestyl. Following oral medication the peak levels are observed in a period of about one hour, and following intravenous medication in a few minutes. After intramuscular injections there is an appreciable level at five minutes with a gradual increase at the fifteen- and thirty-minute periods. (Figs. 1 to 6.) The peak level is obtained in about fifteen minutes to one hour. The rate of decline in serum concentration in the normal control group is quite gradual and in a general way is similar to that seen when the drug is administered by the oral route.

From the standpoint of toxicity the intramuscular method of administration compares quite favorably with the oral route and is

TABLE II

TREATMENT OF ARRHYTHMIAS WITH INTRAMUSCULAR PRONESTYL PREPARATIONS

Case	Age and Sex	Arrhythmia	Dose and Preparation	Results	Remarks
1, B. G.	80, F	Auricular flutter	1 gm. P.HCl	Flutter persisted but auricular rate was slowed; ventricular rate was increased	Subsequently rhythm was changed to auricular fibrillation with digitalis and converted to N.S.P. when digitalis was stopped
2, W. H.	49, M	Auricular flutter	1 gm. P.HCl	Converted to N.S.R. in 30 minutes	Previously had been on quinidine gr. III three times a day for 6 days with no effect
3, J. S.	43, M	Auricular flutter	1 gm. P.HCl	Flutter persisted but auricular rate was slowed; ventricular rate was slightly increased	Subsequently rhythm was changed to auricular fibrillation with digitalis
4, O. K.	53, M	Supraventricular tachycardia, probably auricular flutter	1 gm. P.HCl	Converted to auricular fibrillation with paroxysms of flutter and auricular tachycardia in 10 minutes and N.S.R. with frequent A.P.C. in 20 minutes	This patient manifested all the auricular ectopic arrhythmias during conversion to N.S.R.
5, H. B.	54, M	Nodal tachycardia	1 gm. P.HCl	Converted to N.S.R. in 30 seconds	Pronestyl may inadvertently have entered a vein accounting for rapid conversion
6, J. W. Jr.	62, M	Nodal tachycardia	1 gm. P.HCl	Converted to N.S.R. in 3 minutes	None
7, W. S.	64, M	Nodal tachycardia	1 gm. P.HCl	Converted to N.S.R. in 18 minutes	None
8, J. H.	68, M	Bigeminal rhythm due to A-V nodal extrasystoles	1 gm. P.HCl	Converted to N.S.R. with occasional nodal extrasystoles in 10 minutes	None
9, S. P.*	66, F	Bidirectional ventricular tachycardia, auricular fibrillation	1 gm. P.HCl	Ventricular tachycardia stopped in 5 minutes; auricular fibrillation persisted	Infrequent V.P.C. persisted
10, E. M.†	81, F	Ventricular tachycardia, auricular fibrillation	1 gm. P.HCl	Ventricular tachycardia stopped in 15 minutes; auricular fibrillation persisted	No recurrence of ventricular tachycardia while maintained on pronestyl
11, B. S.	13, M	Ventricular tachycardia; paroxysmal	0.5 gm. P.HCl	Paroxysms of ventricular tachycardia were abolished in 18 minutes; bigeminal rhythm due to V.P.C. was still present after 40 minutes	Although the V.P.C. were not abolished, the patient did not have the tachycardia while under the influence of the drug
12, S. P.*	66, F	Frequent V.P.C., with bigeminy, auricular fibrillation	1 gm. P.HCl	Eliminated V.P.C. in 6 minutes; auricular fibrillation persisted	None
13, S. P.*	66, F	Frequent V.P.C., auricular fibrillation	1 gm. P.HCl	Only rare V.P.C. after 5 minutes; auricular fibrillation persisted	None
14, M. W.	76, F	Frequent V.P.C., with bigeminy, auricular fibrillation	1 gm. P.HCl	Eliminated V.P.C. in 5 minutes; auricular fibrillation persisted	None
15, M. N.	56, F	Occasional V.P.C., auricular fibrillation	0.5 gm. P.HCl	No change in the frequency of V.P.C.	None

TABLE II (*Continued*)

Case	Age and Sex	Arrhythmia	Dose and Preparation	Results	Remarks
16, L. M.	20, M	Frequent V.P.C., auricular fibrillation	1 gm. P.HCl	V.P.C. increased in frequency with paroxysms of ventricular tachycardia in 15 minutes; V.P.C. were reduced but still more frequent than in the control tracing at 6 hours; auricular fibrillation persisted	Patient died 43 hours after injection (refer to text)
17, J. McC.*	48, M	Frequent V.P.C., with bigeminy, auricular fibrillation	0.5 gm. P.HCl	Stopped bigeminy in 5 minutes; occasional V.P.C. and auricular fibrillation persisted	None
18, J. Wa.	49, M	Frequent V.P.C., with bigeminy	1 gm. P.HCl	Stopped all V.P.C. in 7 minutes	Subsequently was maintained on oral pronestyl with no recurrence
19, E. M.†	81, F	Frequent V.P.C., auricular fibrillation	1 gm. P.HCl	Diminished number of V.P.C. in 10 minutes; marked effect in 30 minutes	V.P.C. reappeared in 6 hours and a similar response was noted following 2 subsequent injections
20, H. S.	72, M	Frequent V.P.C.	1 gm. P.HCl	No significant change	None
21, A. L.†	52, M	Frequent V.P.C., with bigeminy	1 gm. P.HCl	Only rare V.P.C. persisted after 10 minutes	V.P.C. reappeared in 6 hours and a similar response was noted after a second injection
22, A. W.	50, M	Frequent V.P.C.	1.5 gm. P.Gluc.	Diminished number of V.P.C. in 10 minutes and marked effect in 30 minutes	Subsequently maintained on oral pronestyl
23, A. L.†	59, M	Frequent V.P.C., with bigeminy	1 gm. P.HCl	Diminished number of V.P.C. in 30 minutes and marked effect in 1 hour	Subsequently maintained on oral pronestyl
24, L. C.	55, M	Occasional V.P.C., auricular fibrillation	1 gm. P.HCl	Diminished number of V.P.C. in 30 minutes; no effect on auricular fibrillation	Patient died while on oral pronestyl with N.S.R. and widened QRS intervals
25, S. I.	65, M	Occasional V.P.C.	1 gm. P.HCl	Eliminated V.P.C. within 30 minutes	None
26, R. McC.	61, F	Frequent V.P.C., with bigeminy, auricular fibrillation	0.5 gm. P.HCl	Diminished number of V.P.C. in 30 minutes; no effect on auricular fibrillation	After a total of 1 gm. P.HCl intramuscularly, V.P.C. were greatly diminished at 8 hours, and eliminated in 16 hours after a total of 1.5 gm
27, J. McC.†	48, M	Paroxysmal auricular tachycardia with frequent V.P.C.	1 gm. P.HCl	Converted to N.S.R. in 8 minutes with elimination of V.P.C.	Paroxysms had lasted 3 days without converting on C.S.P. and prostigmine plus C.S.P.
28, L. C.	84, F	Paroxysmal auricular tachycardia	1 gm. P.HCl	Converted to N.S.R. between 1 and 2 hours	The conversion cannot definitely be ascribed to the effect of pronestyl
29, R. T.	59, M	Paroxysmal auricular tachycardia with 2:1 A-V block	1 gm. P.HCl	Ventricular rate doubled due to development of 1:1 response	Subsequently converted to N.S.R. with lanatoside C

N.S.R. = normal sinus rhythm
V.P.C. = ventricular premature contractions
A.P.C. = auricular premature contractions
C.S.P. = carotid sinus pressure
P.HCl = pronestyl hydrochloride
P.Gluc. = pronestyl gluconate
* Studied on three different occasions.
† Studied on two different occasions.

superior to the intravenous route. Because of this we are of the opinion that the intramuscular route is the preferable mode of administration in those cases of ectopic rhythms in which prompt alleviation of the arrhythmia is desired. An initial dose may be given intramuscularly to stop the ectopic rhythm and maintenance continued by the oral route. Intramuscular administration is also of value when oral medication is impractical due to unconsciousness or vomiting. This method avoids the sudden peak level following intravenous administration, is accompanied with fewer side effects and accomplishes its effect with sufficient rapidity for the treatment of the majority of cases of ectopic rhythms. It is our impression that the results obtained by the intramuscular method of administration compare favorably in efficacy with those obtained by the intravenous method.

SUMMARY

Our experience is reported with the use of pronestyl gluconate and pronestyl hydrochloride administered by the intramuscular route. These compounds may be given intramuscularly with little or no discomfort or local irritation.

Various doses of the two drugs were given in single injections to normal subjects and patients with congestive heart failure accompanied with varying degrees of renal insufficiency. In addition, pronestyl hydrochloride was administered intramuscularly in multiple doses to a group of normal subjects and patients with congestive failure. Both drugs were used intramuscularly in the treatment of ectopic rhythms.

Determination of serum levels indicates that absorption by this route is quite satisfactory. An appreciable level is observed within five minutes and peak levels are observed usually at fifteen minutes to one hour, after which the serum levels decline slowly. A significant level is still observed after a six-hour period. Higher serum levels and a slower rate of decline were noted in patients with renal insufficiency. The toxic effects as observed in our study are generally mild and compare favorably to those following the oral route of administration. The severe hypotension which occasionally follows intravenous administration was not seen.

The efficacy of the drug given intramuscularly in the treatment of arrhythmias is similar to that observed when it is given orally and intravenously. When given intramuscularly, however, pronestyl has a more rapid action than with the oral route and a slightly slower action than with the intravenous route.

Although the intravenous route may be used for the occasional instance in which an extremely rapid effect is desired, it is believed that the intramuscular route is the preferred one for routine parenteral administration of this drug.

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Infectious Mononucleosis*

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INFECTIOUS mononucleosis has long been known to be particularly prevalent among collegians. Reports have appeared based on experiences at the U. S. Naval Academy,[1] Dartmouth College,[2] Harvard University,[3] Yale University[4] and Smith College[5] as well as reports based on experiences on Army posts,[6] where the great preponderance of the population is also of collegiate age.

Experiences at this hospital have been similar to those of Berberich and Thomas[1] who saw thirty-five cases at the U. S. Naval Academy Hospital over a period of seventeen months, in that about twenty-five to thirty patients with mononucleosis are admitted annually. After seeing about fifty patients it appeared that some of my observations were not in concord with generally held conceptions; therefore a reappraisal of this disease, with emphasis on diagnostic criteria, clinical manifestations and infectiousness, seemed desirable. Accordingly in 1949 I began to analyze and tabulate data in every instance of this disease, as well as examining and following the course of patients. The results of these observations are stated in this article. In addition, a new evaluation of clinical manifestations, hematology, serology, diagnostic requirements and infectiousness is presented. Revisions of several commonly held conceptions are proposed.

Hospital and follow-up studies of cadets are facilitated by their being subject to military discipline. Unlike soldiers, who are frequently moved, cadets remain here for four years, so the problems of transfer to other posts are not encountered and follow-up is easier. Cadets are encouraged to report for medical attention; consequently, patients with mononucleosis are usually seen early. The physical status of cadets is more uniform than that of civilian collegians or enlisted men, and their environment is much more uniform and rigidly controlled. Finally, all of the patients were examined and followed by the author. Therefore, fewer variables were encountered in this study than in most reported series of cases.

CLINICAL OBSERVATIONS

Fifty-six patients were examined and followed. A case was not included unless both serologic and hematologic diagnostic requirements were met, namely, a heterophile antibody reaction in minimal titre of 1:56 of non-absorbed serum and 1:28 in serum absorbed with guinea pig kidney, and over 50 per cent of the leukocytes consisting of lymphocytes with presence of atypical lymphocytes.

Table 1

Subjective Complaints

Symptoms	No. of Patients	Percentage of Patients
Sore throat	39	69.6
Malaise	24	42.9
Headache	21	37.5
Myalgia	7	12.5
Discomfort due to lymph node enlargement	6	10.7
Chills	5	8.9
"Head cold"	4	7.1
Vomiting	3	5.4
Cough	3	5.4
Puffiness about eyes	2	3.6
Diarrhea or increased defecations	2	3.6
Nausea	1	1.8
Arthralgia	1	1.8
Abdominal cramps	1	1.8

Table 1 shows the incidence of subjective complaints on or after admission to this hospital.

Almost all of the patients were admitted two to five days after the initial symptom was experienced. Rarely did admissions occur after six days of illness. Most of the patients with sore

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throats complained of moderate or severe pain. In two instances sore throat was experienced three and six days after admission to the hospital; otherwise sore throat was present on admission. Malaise and headache were almost always moderate. Myalgia, usually mild or moderate, often involved the extra-ocular muscles and occasionally the neck and back. Cough was never a prominent symptom. It is noteworthy that both patients with increased defecations were only mildly ill, had heterophile antibody titers of 1:56 unabsorbed and 1:28 after absorption with guinea pig kidney, and the blood cell findings became normal unusually quickly—three weeks after onset of symptoms.

Table II

Physical Signs

Sign	No. of Patients	Percentage of Patients
Fever during first hospital day	56	100.0
Lymph node enlargement	56	100.0
Pharyngeal or tonsillar inflammation	46	82.1
Severe	22	39.3
Moderate	22	39.3
Mild	2	3.6
Edema of eyelids	19	33.9
Palatal enanthem	3	5.4
Jaundice	2	3.6
Relative bradycardia	2	3.6
Rash	0	0.0

The physical signs observed on admission and during the course of the illness are shown in Table II.

Fever on admission was usually in the range of 100° to 101°F. Pharyngeal inflammation was usually present on admission but in a few cases did not occur until the fifth to seventh day of illness. Tonsils were frequently covered with yellow or gray patches or small membranes. Tonsillar ulceration was less frequent. Lymph node enlargement was usually mild or moderate. Enlargement of posterior cervical lymph nodes was a helpful clue to the correct diagnosis. Anterior cervical lymph node enlargement was of lesser significance since any pharyngotonsillar infection may cause such enlargement. Axillary, epitrochlear and inguinal nodes were enlarged less often and to a lesser degree. Roentgenography, performed on only twenty-one patients, demonstrated enlarged mediastinal lymph nodes in three cases. As stated by Bernstein,[7] lymph node enlargement is transient in some cases; therefore, if patients are not examined daily, mild enlargement may be overlooked. Duration of enlargement was variable. No patient had more than mild enlargement when discharged. Suppuration never occurred.

Supra-ocular edema, present early in the course of illness, should be emphasized more as a helpful sign. It consists of a drooping of the swollen orbital portion of the upper eyelid upon the palpebral portion, and sagging of the latter, which is also swollen, resulting in a narrower ocular aperture. This sign is shown in the accompanying illustrations. (Figs. 1 and 2.) One patient stated that on the morning of admission a roommate had asked whether he was going to give his orders in Chinese (because supra-ocular edema, obscuring the upper lids, had given his eyes an oriental appearance). Frequently, supra-ocular edema was observed by the admitting nurse and the patient brought to my attention as possibly having mononucleosis. More often than not, such a patient had the disease.

Although palatal enanthem was noted by me in only 5.4 per cent of the present series, I was impressed, as were Berberich and Thomas at the Naval Academy, before beginning this investigation with an even greater frequency. The enanthem consisted of about five to twenty pinhead sized, red spots which darkened in about forty-eight hours and disappeared after about three or four days. Its appearance was always a fruitful clue.

Jaundice was never present on admission; it was observed first during the latter half of the second week of illness. Liver involvement without apparent jaundice is probably present to some degree in almost every case of mononucleosis.[8] Cutaneous changes except for erythema were not observed in any patient. Although myalgia of the neck muscles was occasionally present, unquestionable nuchal rigidity was never observed. Splenic enlargement was palpable or demonstrable by roentgenography in many cases. However, an accurate statement concerning the incidence of splenic enlargement in mononucleosis entails careful, daily examination of the spleen and also involves the imponderable elements of the examiner's technic, experience and imagination.

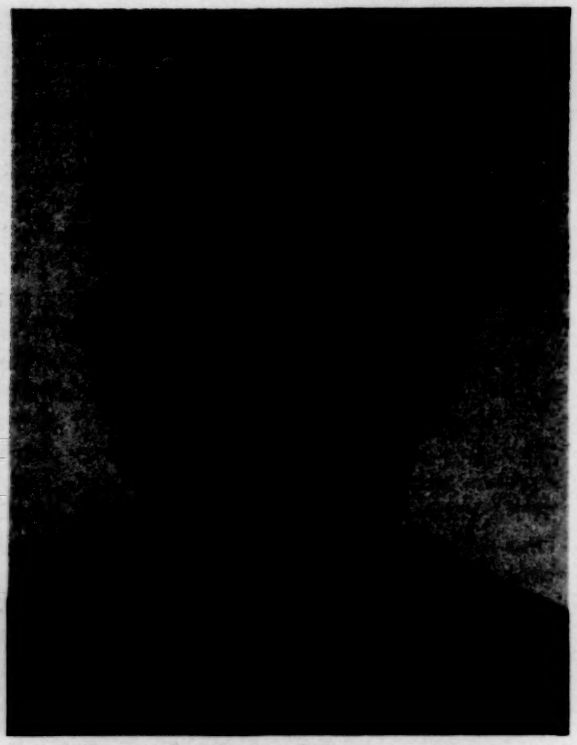

FIG. 1. Eyes on fourth day of illness; note obscuring of upper eyelid by fold of sagging tissue above lid.

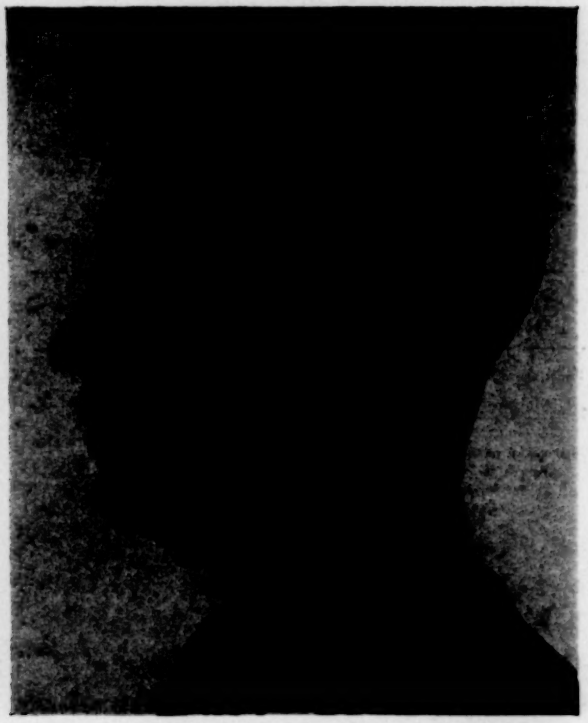

FIG. 2. Profile of eyes on fourth day of illness; note drooping upper eyelid, narrow ocular aperture and generalized puffiness of face.

Therefore, the incidence of splenic enlargement is not stated in numerical terms.

Although the adjective protean has been used in connection with the clinical picture in almost every report of mononucleosis, the clinical manifestations encountered in this series of patients could easily be grouped into two major clinical syndromes, shown in Table III.

Table III

Clinical Syndromes

Syndrome	No. of Patients	Percentage of Patients
Pharyngeal	44	78.6
Typhoidal	11*	19.6
Gastrointestinal	1	1.8

*Pharyngeal manifestations appeared between fifth and seventh days of illness in three patients.

The vast majority of the patients, 78.6 per cent, had the pharyngeal syndrome—fever, sore throat, headache and malaise; and examination on admission or within a few days disclosed enlargement of the posterior cervical and other lymph nodes. Such manifestations, if not accompanied by leukocytosis and polynucleosis, would almost always lead to a diagnosis of mononucleosis meeting the hematologic and serologic criteria stated above. Indeed, merely the combination of inflamed, ulcerated or exudate covered tonsils and normal hematologic findings is a good basis for suspecting mononucleosis and instituting necessary tests, inasmuch as most diseases in which such tonsils are seen are accompanied by leukocytosis and polynucleosis.

Patients with the "typhoidal" syndrome complained only of feverishness, malaise and headache; and examination on admission or later revealed no abnormalities except fever, enlargement of lymph nodes in every case, and in some cases splenic enlargement or the characteristic eyes.

The one patient manifesting predominantly gastrointestinal symptoms complained of chilliness, nausea, mild, generalized abdominal pain and increased, although not watery, defecations. Examination revealed only mild cervical and axillary lymph node enlargement. However, he had an elevated temperature for nine days;

blood count disclosed a peak of 72 per cent lymphocytes (total leukocyte count of 3,500) with many atypical lymphocytes. The heterophile test was positive in a dilution of 1:56 of unabsorbed, and 1:28 of guinea pig absorbed serum. Twenty-one days after onset of illness positive heterophile reactions were present only in dilutions of 1:28 and 1:14, respectively.

Table IV

Duration of Illness

Days of Illness	No. of Patients	Percentage of Patients
4 - 7	11	19.6
8 - 14	29	51.8
15 - 21	11	19.6
22 - 28	5	9.0

Duration of illness, analyzed in Table IV, was observed as closely as possible. This feature cannot, of course, be described with mathematical accuracy because there is a gradual disappearance of many symptoms. However, after temperature had returned to normal and remained so for twenty-four hours, and if there were no complaints, it was concluded that the illness had ceased. Several patients did not feel entirely as well as they had before becoming ill; however, no patients complained of excessive weakness or of other symptoms despite return to vigorous cadet activities within one to four weeks after temperature became normal. Many of these patients were followed for two years, and all were followed for at least three months. Yet none had persistent fatigue, aching of the legs or weakness mentioned by Isaacs.[9] It is possible that the average patient with mononucleosis might be ill slightly longer than these cadets, who were in the prime of life and in superlative physical condition. On the other hand, the average patient is not required to live the relatively Spartan life of a cadet.

HEMATOLOGY

Lymphocytes constituted over half the total of white blood cells at some stage of the illness in all patients, as shown in Table V. Lymphocytosis was found on the very first blood count in 70 per cent of patients. In most of the rest, with initial findings within the range of normal, the second blood count revealed lymphocytosis. It was of interest to determine when leukocytes became preponderantly lymphocytes. Tables VI A and B disclose that lymphocytosis occurred as early as the second day of illness, and in 46 patients (82.1 per cent) occurred during the first week. Ten patients (17.9 per cent) did not show lymphocytosis until the second week of illness. The latest appearance of lymphocytosis occurred between the twelfth and fourteenth days. In no instance did neutrophiles at any time constitute over 77 per cent of the leukocytes.

Table V

Lymphocytosis

Highest Percentage of Lymphocytes	No. of Patients*	Percentage of Patients
51 - 59	4	7.1
60 - 69	10	17.9
70 - 79	27	48.2
80 - 89	14	25.0
90 - 99	1†	1.8

*Almost all patients had between five and nine blood counts.
†This patient had 91 per cent lymphocytes of total leukocyte count, which was 22,000.

Atypical lymphocytes were usually detected at the same time as lymphocytosis. However, in some instances they were not seen until a few days afterward. Atypical lymphocytes were observed in every case.

Duration of lymphocytosis and of presence of atypical lymphocytes was variable. Usually both were present for at least two weeks, and usually they disappeared before two months. The shortest duration of lymphocytosis was nine days and the longest was over one hundred six days. The earliest disappearance of atypical lymphocytes was between the thirteenth and sixteenth days. The longest duration was over one hundred three days.

Inasmuch as almost no information has been published concerning the erythrocyte sedimentation rate in mononucleosis, data were accumulated regarding the results of this test. Sedimentation rates were determined on blood specimens of thirty-six patients; half had accelerated and half had normal sedimentation. Half of the patients showing rapid sedimentation had normal rates during the first week of illness but during the second and third weeks acceleration occurred. Extremely rapid sedimentation was rarely encountered; increased rates were

usually only about 18 to 22 mm. per hour (Wintrobe method).

SEROLOGY

The diagnostic value of the heterophile antibody reaction was underscored when investigations and analyses of cases without characteristic symptomatology invariably led to negative results of heterophile tests; such patients did not usually have characteristic hematologic findings. Conversely, not one patient found to have a characteristic clinical and blood picture failed to develop a positive reaction in a titer of at least 1:56 in non-absorbed and 1:28 in guinea pig kidney absorbed serum. Usually the titer of a serum after absorption with guinea pig kidney was half that of unabsorbed serum, but occasionally titers were equal. Table VII shows how titers of unabsorbed serum were distributed.

The observation of Bernstein, that the heterophile reaction was usually positive when first performed, was confirmed, as shown in Table VIII. In the two cases in which heterophile tests performed initially in the first week were negative, the results in the second week were positive; accordingly, of forty-three patients who had heterophile tests performed in the first two weeks, positive results were obtained in 95.3 per cent. Therefore, if a heterophile test is not positive by the fourteenth day of illness, it is very infrequently positive thereafter. When two or more heterophile tests were performed, a comparison was made to see when the highest titer was found. Of twenty cases which could be used for such a study four patients had a higher titer during the first week of illness than subsequently; ten patients showed the highest titer in the second week of illness, that is, higher than in the first week and not exceeded thereafter; and six patients had a higher titer in the third week than during the first or second weeks. The remaining cases of this series were not revealing in that equally high titers were found on two successive weeks, or only one heterophile test was done during the early period of illness, or the first heterophile test was taken after the third week of illness.

The duration of positive serologic findings

Table VI

Appearance of Lymphocytosis*

A			B	
Initial Examination (Day of Illness)	No. of Patients	No. Showing Lymphocytosis	Shift to Lymphocytosis (Days of Illness)	No. of Cases
2nd	1	1	Between 3rd and 5th	1
3rd	8	7	Between 4th and 5th	2
4th	11	6	Between 4th and 6th	1
5th	12	8	Between 4th and 8th	1
6th	5	4	Between 4th and 10th	1
7th	8	4	Between 5th and 6th	2
8th	1	0	Between 5th and 7th	2
9th	4	3	Between 6th and 9th	1
10th	1	1	Between 7th and 8th	2
11th	1	0	Between 7th and 10th	1
12th	1	1	Between 7th and 13th	1
13th	1	1	Between 8th and 9th	1
18th	1	1	Between 9th and 10th	1
24th	1	1	Between 11th and 14th	1

*Defined as lymphocytes comprising over 50% of total leukocyte count.

(defined in Table VII) was variable. Usually the heterophile reaction was positive for at least three weeks and often for over one month. However, several patients had early changes from above to below the critical titer: between seventh and tenth, eighth and twenty-first, and tenth and thirty-second days. In several instances titers changed between the twenty-sixth and forty-fifth days. Determination of how long the reactions remained diagnostically positive was less easily ascertained. However, in one case the change occurred between the seventy-second and ninety-third days. This was the latest recorded positive reaction. In other instances of long duration of a positive heterophile reaction the titer fell below the critical level between the fifty-seventh and ninety-sixth, the forty-seventh and ninety-fourth, and the forty-fifth and fifty-third days.

Table VII

Highest Heterophile Antibody Titers

Titer	No. of Patients	Percentage of Patients
1:56	7	12.5
1:112	12	21.4
1:224	12	21.4
1:448	10	17.9
1:896	5	8.9
1:1792	7	12.5
1:3584	3	5.4

Table VIII

Appearance of Positive Heterophile Titer

Stage of Illness	Tested for First Time	Positive Results* No.	%
First week	11	9	81.8
Second week	31	31	100.0
Third week	12	11†	92.0
After third week	2‡	2	100.0

*Defined as titer of at least 1:56 with unabsorbed serum and 1:28 with serum after absorption by guinea pig kidney.
† Patient with negative result had a negative heterophile on the fifteenth day of illness; he was not tested again until the forty-second day after illness began when results were positive.
‡ One patient was tested initially on the twenty-third day; another on the thirty-fifth day.

EPIDEMIOLOGY

The mode of transmission of infectious mononucleosis is not certain although it is generally regarded as a disease contracted through the respiratory passages. As stated by Evans,[10] despite increasingly voluminous reports concerning this disease the publications dealing with alleged epidemics are few.

Starting with the first cases observed early in 1946, I was on the alert for cases occurring in roommates. Almost all cadets live in relatively small rooms, three to a room. Head colds, influenza, mumps and other respiratory diseases are readily transmitted from one roommate to another. However, in six years I have not observed a single instance of mononucleosis occurring in a roommate of a patient.

Despite interrogations of many patients I could never establish a source of infection until fairly recently a clue was obtained. A patient became ill on February 8, 1951. He stated that on December 23, 1950, he was on a train and spent about twelve hours in the company of a female medical student whom he had never seen before and whom he never saw afterward but with whom he corresponded. During this time there was kissing between these two individuals; and they also carelessly drank refreshments from drinking vessels passed around among a group of train acquaintances. This patient learned from his medical student train acquaintance that she had become ill with a disease diagnosed, in a university hospital, as infectious mononucleosis, and that the onset of her symptoms antedated the onset of his symptoms by two or three days. It seems likely that either the patient and his train acquaintance were infected from the same source or that the patient acquired the disease from the medical student, who was in the very earliest phase of the incubation period on December 23, 1950. The inference—that of a relatively long incubation period—is novel.

COMMENTS

A great deal of confusion and many contradictions exist in the literature concerning mononucleosis. In an endeavor to bring some order out of chaos, comments will be made under five headings: the clinical picture, hematology, serology, epidemiology and diagnostic criteria. Some of the confusing and contradictory aspects of this disease which require clarification are, first, the oft repeated statement that the disease is protean and the observations presented in this

study, and the experiences of several authors mentioned below, that the great majority of patients have clinical manifestations resembling either pharyngotonsillitis or typhoid fever; second, the variable diagnostic importance of the heterophile reaction illustrated by the exclusion of all cases without positive heterophile antibody reactions from series reported by authors such as Read and Helwig and Berberich and Thomas contrasted with a report of an epidemic of mononucleosis involving sixteen children none of whom had positive heterophile antibody reactions[11] and reports wherein positive heterophile reactions occurred in only 60 and 72 per cent of cases;[4,6b] third, the excessive diagnostic importance attributed to atypical lymphocytes *per se*[6d] contrasted with the experience of many investigators, mentioned below, showing that this blood cell is non-specific; and fourth, the experience of many observers at various universities,[12] as well as my own, that spread from one person to another is uncommon and its occurrence in roommates almost unknown contrasted with reports of epidemics.[13]

Clinical Picture. Gorham,[14] in a textbook discussion of the clinical manifestations of mononucleosis, stated that the great majority of cases fell into two clinical group—the pharyngeal and the lymphatic or Pfeiffer. Inasmuch as lymph node enlargement is common to all patients, cases falling into the lymphatic group could be classified as pharyngeal or typhoidal depending on prominence of pharyngitis.

In this series of cases the clinical picture was not remarkably variable; all the patients but one could easily be classified into two clinical groups. An analysis of literature shows that although the adjective protean has become almost inescapably connected with descriptions of mononucleosis, many authors report that the pharyngeal syndrome was seen in the great majority of cases. For example, 77 per cent of Bernstein's series of sixty-five patients showed signs of pharyngitis and all but three complained of sore throat. Milne reported that sore throat was by far the outstanding single complaint. Berberich and Thomas stated that the most frequent complaint was sore throat, and the most frequent physical finding was reddening of the posterior pharynx with lymphoid hyperplasia. They did not give statistical frequency of signs and symptoms. Mitchell and Zetzel, in a study of twenty-five cases, stated that sore throat was the presenting symptom in 64 per cent of cases and that the admission diagnosis was either nasopharyngitis or infectious mononucleosis in 80 per cent. Indeed, 92 per cent of their cases had admission diagnoses of nasopharyngitis, mononucleosis or cervical adenitis. It is hard, therefore, to understand the statement by these authors that mononucleosis may assume the guise of almost any known disease varying from psychoneurosis to meningitis. The cases reported in their series did not substantiate this description. Another report[6e] of sixty-three patients, although mentioning wide variability in the type and severity of symptomatology of infectious mononucleosis, stated that 81 per cent showed pharyngitis or tonsillitis on admission or during the course of hospitalization. Read and Helwig, in an analysis of 300 cases, stated that the most frequent complaints were sore throat, enlarged lymph nodes, headache and fever.

Various syndromes are mentioned in the literature; however, most terms are confusing. For the purpose of clarification and to facilitate clinical approach classification of cases into pharyngeal and typhoidal syndromes seems simplest and most practical. Almost every case can be classified thus. I believe that the concepts of a glandular, sometimes called lymphatic or Pfeiffer, syndrome and of a febrile syndrome are not fruitful because practically all cases have both fever and enlarged lymph nodes.

There are other clinical manifestations which deserve specific mention. Abdominal pain of a severity to suggest acute appendicitis is rare.[7] It was never encountered in this series, nor was it mentioned by Read and Helwig or by Milne as an admission diagnosis. Almost all the reports in the literature agree on this point. Yet acute appendicitis is mentioned as a differential diagnosis to be considered by Wechsler et al. and by Gardner and Paul. As will be pointed out repeatedly, the articles stressing unusual manifestations are those in which diagnostic criteria were inadequate. In the large series reported by Wechsler et al. cases were included if they met either of only two diagnostic requisites: hematology showing at least 10 per cent atypical lymphocytes (of the total leukocyte count) or a positive heterophile reaction in a high titer. In the series of Gardner and Paul one of the lowest percentages of positive heterophile tests, 60 per cent, was reported.

Results of my investigations agree with the findings of Bernstein that meningitis is rarely encountered in mononucleosis. He did not men-

tion it in any of the sixty-five cases in his own series. Read and Helwig found that meningitis was suspected in only three of 300 cases analyzed by them, and Berberich and Thomas did not suspect meningitis in any of their cases. Consequently, when my series of cases is added to the two last named (in all three all patients had positive heterophile antibody reactions), a total of 391 cases of mononucleosis with 100 per cent serologic confirmation yielded only three cases of suspected meningitis and these three were suspected only on admission. Yet reading the literature on mononucleosis creates an erroneous impression that in cases of meningitis in which the predominant cell in the spinal fluid is the lymphocyte, the diagnosis of mononucleosis must be seriously considered.

The results of this investigation are in accord with the observations of Bernstein regarding the rare occurrence of diarrhea and also regarding the unusual occurrence of joint pains. Also as stated by him, relative bradycardia is seen not infrequently. His belief that lymph nodes are almost always felt if searched for often and carefully enough was confirmed.

Rashes are stated to occur frequently in mononucleosis. However, in this series none except transient erythema were observed. In reports of mononucleosis in which all patients had positive heterophile antibody reactions the incidence of rashes is relatively low. Berberich and Thomas stated that it was the least frequent physical sign but exact figures were not given. Read and Helwig state that 5 per cent had "dermatitis." Milne in a series characterized by a positive heterophile reaction in 90 per cent of patients tested found a transient "faint erythematous rash" in 4.5 per cent and a more obvious rash in only 3.6 per cent. On the other hand, series in which the percentage of positive heterophile antibody reactions were relatively low contained greater numbers of patients with skin changes. For example, Mitchell and Zetzel, reporting a series of cases in which the heterophile reaction was positive in only 72 per cent, observed rashes in 20 per cent of cases. Templeton and Sutherland[15] found rashes in 18.5 per cent of ninety-one cases of mononucleosis but did not report on heterophile tests or other diagnostic criteria.

My observations concerning the duration of mononucleosis were in accord with those of Bernstein, who stated that in general the acute febrile stage lasted seven to twenty-one days, and Berberich and Thomas, who stated that the typical patient was sick for about two weeks. Seventy-one and four-tenths per cent of the patients in this series were ill between four and fourteen days and 91 per cent were ill less than three weeks. No patient was ill longer than four weeks. Most observers reported similarly.

Bernstein stated that a true chronic form of mononucleosis has not been recognized, but that lymph node and splenic enlargement and atypical lymphocytes could persist for months or years. However, Isaacs stated that of a group of 206 patients who had infectious mononucleosis fifty-three had symptoms persisting from three months to at least four years. The syndrome included fatigability, depression, afternoon elevation of temperature, exhaustion, weakness and aching of the legs. These symptoms are obviously common to a great many organic and psychic illnesses and have no significance without documentation. The only requirement for diagnosis was the presence of "infectious mononucleosis cells" in the blood. The evidence presented by the author to link causally the above syndrome to mononucleosis is inadequate. Follow-up of the patients seen here, in many instances for two and three years, before and after tabulation of data was started revealed no instances of chronic mononucleosis.

Hematology. Relative lymphocytosis and the presence of atypical lymphocytes in blood smears are characteristic findings in mononucleosis. However, these changes are non-specific. We have frequently had patients with various upper respiratory diseases whose blood contained such cells, but heterophile antibody reactions were uniformly negative in ten such patients. A similar experience was reported by Halcrow, Owen and Rodger[16] who found four cases of atypical pneumonia with absolute lymphocytosis and abnormal lymphocytes. In all four cases the heterophile test was negative and glandular enlargement was absent. They stated further that in rubella abnormal lymphocytes resembling those of infectious mononucleosis are present; and this statement was also made by Benjamin and Ward.[17] Wechsler, Rosenblum and Sills cited five reports[18] concerning the discovery of atypical lymphocytes in diseases other than mononucleosis. Goldthwaite and Elliot[19] cited two additional authors[20] who reported on the finding of atypical lymphocytes in infectious hepatitis. Evans[8a] stated that hematologic pictures of both experimentally induced and

naturally acquired acute hepatitis may simulate mononucleosis and as many as 60 per cent atypical lymphocytes have been described.

Just as the human body responds to a variety of noxious agents, notably various bacteria, with leukocytosis and polynucleosis, probably it responds to another group of noxious agents (perhaps viruses) with absolute or relative lymphocytosis, and in so doing produces a variety of atypical lymphocytes. At any rate, there is convincing evidence to show that lymphocytosis and atypical lymphocytes are found in diseases other than infectious mononucleosis.

In the literature on mononucleosis one finds almost no mention of the sedimentation test. I could find only one brief mention[6e] in which it was stated that six patients had sedimentation tests; five of the six were elevated (degree of elevation was not stated). Therefore, sedimentation tests were frequently performed to determine whether they could provide fruitful diagnostic clues. Judging by the experience in my series of cases, the sedimentation rate is of negative value, that is, unusually rapid sedimentation rate at any time and moderate acceleration during the first week of illness militate against the diagnosis of mononucleosis.

Serology. The heterophile antibody reaction discovered in 1932 is uniformly stated to be of importance in the diagnosis of mononucleosis. However, there are many conflicting statements regarding onset and duration of positive reactions, level of diagnostic titer and, most important, the weight given to this test as a diagnostic requirement.

The observations tabulated in Table VIII agree with Bernstein's observation that the heterophile reaction becomes positive early in the disease and is usually positive on the first test. All except three patients tested during the first three weeks of illness had positive reactions on the first performance. Two of these patients had second tests within the first three weeks and results of these were positive. The remaining patient was tested for the first time on the fifteenth day of illness, then not until the forty-second day after illness began. The result of the second test was positive. These findings are also in accord with those of Kaufman[21] who reported on fifty-one heterophile reactions. Only two patients with negative reactions after the twenty-first day of illness had positive reactions at a later date. My observations were in general agreement with those of Bernstein and Kaufman in that the duration of a positive heterophile reaction was most variable, persisting usually for at least three weeks and often for over one month, and remaining positive as late as the seventy-second day after onset of illness. The earliest fall from a diagnostic titer to a subcritical titer occurred between the seventh and tenth days of illness. In one instance the titer changed between the eighth and twenty-first and in another between the tenth and thirty-second days.

In referring to positive reactions or diagnostically critical titers, reference is made to a titer of 1:56 of unabsorbed and 1:28 of guinea pig kidney absorbed serum. Correlation of the clinical data, hematology and serology led to this conclusion which is in agreement with that of Kaufman. Read and Helwig and Berberich and Thomas chose titers of 1:112 of unabsorbed serum, but did not rely on the guinea pig absorption tests and made no attempt to arrive at a minimal titer of diagnostic significance. Kruger, Wallace and Penchansky stated that a dilution of 1:112 constituted a diagnostic titer, but again did not rely on guinea pig absorption tests.

Falsely positive tests were found by Kaufman and others to occur in patients who had recent injections of horse serum. In addition, he found that Hodgkin's disease, rubella and injections of liver extract give positive heterophile antibody reactions in a dilution of 1:56 or higher. However, patients in these three categories did not have positive serologic findings after guinea pig kidney absorption. No other conditions have been associated with false positives except that Wechsler, Rosenblum and Sills found three patients with atypical pneumonia whom they did not regard as having mononucleosis, with positive heterophile reactions. In the first instance the agglutination rose from 1:28 to 1:224; in the second instance the titer remained stationary at 1:112; and in the third instance the titer rose from 1:112 to 1:224. Despite repeated blood studies, abnormal lymphocytes and relative lymphocytosis were not observed by these authors. The sera of two of these patients were tested and did not show positive heterophile antibody reactions after absorption with guinea pig kidney. These authors cite other instances of increased heterophile antibody titers in virus pneumonia.[22]

As this investigation continued the correlation between a positive heterophile reaction and the diagnosis of mononucleosis became more and

more convincing. It was invariably observed that patients with uncommon clinical manifestations—under consideration as mononucleosis cases because atypical lymphocytes or merely increased numbers of lymphocytes were reported in hematology—turned out to have negative heterophile antibody reactions. Almost invariably patients with the group of clinical manifestations termed the pharyngeal syndrome not associated with polynucleosis were found to have positive heterophile reactions; and without exception patients with both typical symptomatology and typical hematology were found to have positive heterophile antibody reactions.

Although this paper places diagnostic emphasis on the positive heterophile antibody reaction, it is thought that positive reactions may occur in conditions other than mononucleosis. As mentioned previously, Kaufman and others found positive reactions in a small group of conditions. In addition, it is believed possible that outbreaks of subclinical disorders, with hematology and serology resembling mononucleosis, are really different disease entities, perhaps caused by microorganisms closely related to the causal agent of mononucleosis or by a different strain of the same organism. This conjecture is based on the fact that the heterophile antibody reaction is, after all, a non-specific test.

Epidemiology. One of the most baffling aspects of mononucleosis is the variance between reports of occurrences of epidemics and, on the other hand, failure of experimental attempts to transmit the disease to man as well as the experiences of investigators at many American universities agreeing on the virtual absence of spread among roommates or other close contacts. In an attempt to cast a little light on this puzzle, pertinent literature was analyzed.

Reports of epidemics prior to the development of the heterophile antibody test by Paul and Bunnell in 1932 must be excluded from consideration of epidemiology inasmuch as the diagnosis of mononucleosis cannot be relied upon. Typical of reports of such epidemics is that of Tidy and Daniel[23] who reported an epidemic of twenty-five cases in 1923. These patients had lymph node enlargement, but hematology was not characteristic in that only one patient's blood contained over 60 per cent lymphocytes and only six additional patients had 50 per cent of more lymphocytes. Furthermore, typical of reports of epidemics, clinical manifestations were not those usually observed; and constitutional symptoms and pharyngitis were not pronounced. It is interesting that Tidy[24] many years later mentioned the value of heterophile tests in epidemics.

Nolan[25] in 1935 reported a "so-called epidemic of glandular fever." He reported on 222 patients; almost all were children. In only forty instances were heterophile tests done; the guinea pig kidney absorption technic was not used. The symptom complex reported was most unusual for mononucleosis: fretfulness, change in personality, fever, pain in neck. There was no mention of physical signs; and it appears that many patients were never seen and none were examined by the author while they were sick. Hematology disclosed a startling increase of abnormal lymphocytes; and "lymphoblasts" were seen in 35 per cent of cases with "abnormal monocytes" reported in 80 per cent. Details of cases were not given. It is highly questionable whether this was an epidemic of mononucleosis. The description is inadequate to substantiate a diagnosis of this disease; and the blood cells reported are not common in mononucleosis. This report illustrates that studies showing a high incidence of unusual symptoms, or mild or subclinical cases, or contagiousness contain a low incidence of positive heterophile antibody reactions. Goldthwaite and Elliott reported what they termed a mild clinical and subclinical epidemic most probably of infectious mononucleosis in a small detachment of men. During the course of the winter every member of a group of twenty-six men showed atypical lymphocytes in his blood smear. However, symptomatology was not characteristic of mononucleosis in that, except for the original patient, only one of four clinically sick patients had sore throats. Furthermore, there were twenty-one subclinical cases. Again it is noteworthy that only the original case had a positive heterophile antibody reaction, and guinea pig absorption was not reported in this case.

Mathers and Evans[26] reported what they termed an epidemic of infectious mononucleosis on a troopship. However, this epidemic consisted of only four patients in the entire ship; and these four officers had in common attended a course which the other shipmates did not attend before boarding ship. It appears that there was a remarkable absence of spread to other individuals in an environment characterized by close contact. Furthermore, it is not certain that these four patients had mononucleosis in that heterophile tests were not performed

and hematology was not characteristic; one patient had only 42 per cent lymphocytes without atypical forms; the second patient had only 23 per cent lymphocytes with aberrant cell forms; the third patient had only 21 per cent lymphocytes (but 31 per cent monocytes) with many aberrant cells; the fourth patient had 23 per cent lymphocytes (and 28 per cent monocytes) without aberrant forms.

Vander Meer, Lutterloh and Pilot reported twenty-six clinical and 340 subclinical cases in an Army camp occurring between December, 1943, and May, 1944. Of these 356 cases there were only twenty-one instances of positive heterophile agglutinations; and only eighteen of these had characteristic blood findings and clinical manifestations. Of the 340 subclinical cases only thirteen had both hematologic and serologic abnormalities indicative of mononucleosis. The correlation of unusual symptoms with relatively low incidence of positive heterophile reactions is exemplified in that only 68 per cent of the clinical cases had positive heterophile tests, but cough was present in 35 per cent and a rash in 30 per cent. These investigators performed blood smears on a military unit of 522 men. Forty per cent of the men had occasional atypical lymphocytes. Only 75 heterophile tests could be done on this group; twelve were termed positive reactions.

In only two epidemics did a relatively large percentage of patients have positive heterophile antibody reactions. However, in both groups heterophile tests after guinea pig absorption were not performed. The first of these epidemics, occurring in a hospital in Britain in 1942, was reported by Halcrow, Owen and Rodger. Clinical manifestations were termed protean; and the disease process was unaccompanied by symptoms in 165 cases. Diagnoses were made by subjecting an entire hospital population to blood examination. Clinical manifestations were unusual in that fever was not a feature except in "anginose" cases, sore throat occurred in only thirty-five instances and only four true anginose cases were seen. This description of clinical manifestations is discordant with the data presented in my investigation and with almost all reported series. Hematology was unusual in that well over half of the patients had less than 50 per cent lymphocytes in their blood smear and in only a few cases did lymphocytes exceed 75 per cent. This combination of predominately subclinical cases, unusual symptomatology in clinical cases, relatively low lymphocytosis (that is, compared with hematology tabulated in Table v and in most reported series) are the bases for speculation that this may not have been mononucleosis—speculation supported by the absence of guinea pig absorption tests. Inasmuch as these patients were members of a hospital population, it is possible that the heterophile agglutinations discovered, and perhaps blood responses also, may have been responses to inoculated material—horse serum or other. It was not stated whether or not these patients had received previous inoculations of any type. At any rate, spread of mononucleosis through the population of a hospital has never been duplicated in any American hospital despite the fact that there are many more hospitals in this country and that patients are almost always, if not always, allowed to remain on open wards.

The epidemic reported by Wechsler, Rosenblum and Sills, which occurred on an Army post between August, 1943, and February 29, 1944, is similar to the epidemic described by Halcrow et al. Twenty per cent of the cases had no clinical manifestations. Many unusual symptoms were encountered. Cough was common and pulmonary signs were present in 30 per cent of the cases. A case was not included unless "leukocytoid" lymphocytes constituted at least 10 per cent of the total white blood cell count except that cases not meeting this requirement were included if the heterophile antibody reaction was positive in a dilution of 1:224 or above. No guinea pig absorption tests were performed. Strikingly similar to the British epidemic, it was found that during the height of the epidemic practically every patient in the hospital showed varying percentages of abnormal lymphocytes in blood smears; and the authors believed that many soldiers on the post had mononucleosis but were without clinical manifestations and hence not hospitalized. Sixty-eight per cent of patients had only 49 per cent or less lymphocytes. Again the combination of large numbers of subclinical cases, unusual symptomatology and relatively low lymphocytosis was encountered. This report differs from reports of other epidemics in that 83 per cent of the patients had heterophile titers of 1:56 or higher. However, guinea pig absorption tests were not performed except in a few instances, and when carried out were not uniformly satisfactory. The authors suggest that the heterophile antibodies in an epidemic differ from those described for sporadic

cases. This is another way of saying that possibly the antigen (that is, the causal agent) was not the same in this epidemic as in sporadic cases, a conjecture supporting my belief that under the heading of mononucleosis we have perhaps considered closely allied diseases caused by closely related microorganisms or by different strains of the same organism.

Contrasted to the reports of the above epidemics are the experiences of many authors reporting from universities on non-contagiousness of mononucleosis. One such report[5] merits more detailed discussion. Inasmuch as reports of epidemics have mentioned large numbers of subclinical cases, it occurred to Evans that possibly for every clinically recognized case encountered in universities there might be many others with inapparent infections and that the sporadic nature of infectious mononucleosis might be more apparent than real since these very mild cases might be undetected. Therefore a search for inapparent infections was made in a dormitory of a college in which five clinical cases had occurred within one month. The five patients and fifty-eight other individuals lived in a dormitory consisting of three housing units (each housing unit had separate kitchen and dining facilities). Each patient was interrogated for symptoms which may have been missed previously; cervical lymph nodes were palpated; hematologic studies and a simplified test for heterophile antibodies were done. Lymphocytes and monocytes constituted over 50 per cent of the total leukocytes in only three of the fifty-eight dormitory residents. However, in these three cases cervical lymph node enlargement was absent and the heterophile test was negative. Moreover, atypical lymphocytes were present in only one blood smear. Two residents had faintly positive heterophile tests but no hematologic or clinical evidence of mononucleosis. These findings are concordant with my findings in a smaller group of cadets. Ten cadets, roommates of patients with mononucleosis, had heterophile tests made within one month of the roommates' admission to the hospital in an endeavor to detect subclinical infections. Three of these patients also had hematologic studies. Heterophile antibody tests were negative in all instances, but one patient's white blood cell count showed 63 per cent lymphocytes of which 1 per cent were atypical.

The failure of Evans and other authors to find inapparent cases of mononucleosis is in accord with Evans' failure experimentally to transmit mononucleosis to volunteers.[27] In his experiments frozen and fresh unfrozen throat washings were sprayed into nose and throat with a hand atomizer, dropped directly into the nose with a pipette, and also gargled and then swallowed. Stool preparations were introduced into the stomach through a tube (after excluding the presence of poliomyelitis virus and pathogenic bacteria). Serum from nine patients was pooled and introduced intranasally, orally, hypodermically and intradermally. Evans stated that strict criteria of successful transmission would include hematology, lymph node enlargement and a rise in heterophile agglutination titer, and that he and other investigators failed to satisfy these diagnostic requirements.

The incubation period of mononucleosis has not been established inasmuch as proved patient to patient transmission is lacking. However, it has been estimated at about eleven days by various authors. It is possible that the incubation period is actually much longer—in the range of five to eight weeks. This possibility is suggested by the above mentioned case in which a brief, non-recurring contact on December 23, 1950, was followed in early February, 1951, by mononucleosis occurring simultaneously in the two individuals who had the contact. This theory gains credibility from a report of Paul[28] who reported on three cases of mononucleosis occurring on board a destroyer. These cases were clinically and hematologically characteristic; and heterophile tests were done on two of them yielding positive results. It was of epidemiologic interest that despite the unusually confining environment of a destroyer, there was no spread of disease. The ship had visited the last port about five weeks previously and thereafter operated in an area which precluded the granting of shore leave. Inasmuch as the three patients lived in entirely different quarters of the ship and had no duty contact, it is likely that they acquired mononucleosis during or before their last port visit more than five weeks before symptoms began.

Diagnostic Criteria. The cases described in this report all met the diagnostic prerequisites of symptomatology, hematology and serology. Other authors such as Berberich and Thomas, Read and Helwig, and DeMarsh and Alt, have also confined their reports to cases meeting all of these requirements. On the other hand, there are many reports in which one or more of these

criteria are not met. For example, one series of 366 cases is reported[6c] in which only twenty-one patients had positive heterophile reactions. Bernstein did not state that positive heterophile reaction was an indispensable requirement for diagnosis but inferred that it was of great diagnostic weight. Kaufman stated that a negative heterophile reaction did not exclude mononucleosis and a positive reaction did not definitely establish the diagnosis.

In studying and reporting on a disease produced by an unknown agent it would seem prudent to adhere to strict diagnostic criteria lest other diseases be included and invalid conclusions be formed. The only disadvantage of excessively strict criteria is potential exclusion of a few cases of the disease, thus decreasing, but only slightly, the number of cases reported. This result is far preferable to the situation at present, that is, the absence of uniformly accepted diagnostic prerequisites, which has resulted in the appearance of articles which are contradictory, confusing and at times even misleading. The diagnosis of mononucleosis rests on a tripod base—symptomatology, hematology and serology. Of these three the two former, as discussed previously, are far from specific. The heterophile test is, as far as is known now, relatively the most specific, especially when performed using both unabsorbed and guinea pig kidney absorbed serum. Therefore it appears wise to regard a positive heterophile reaction as a *sine qua non* for diagnosis. After a review of the literature and my own experience, I believe that we can safely accept a heterophile agglutination reaction in a titer of 1:56 as a diagnostic touchstone if the titer after guinea pig kidney absorption is at least 1:28. The clinical manifestations should include lymph node enlargement and fever at some time during the course of the illness. The hematologic criterion proposed is the presence of "atypical" lymphocytes and lymphocytes constituting more than 50 per cent of the leukocytes at some time during the illness.

Inasmuch as the heterophile reaction is not a specific serologic reaction it is recommended that all three diagnostic requirements be met; that is, that for positive diagnosis the patient have clinical manifestations and serologic and hematologic findings characteristic of mononucleosis. When the same diagnostic standards are used by all investigators, uniform clinical symptoms will be observed, and the word protean may no longer be seen so frequently in connection with mononucleosis. Furthermore, by definition there will be no more reports of subclinical cases. Probably reports of epidemics will rarely, if ever, appear.

CONCLUSIONS

1. Fifty-six cases of infectious mononucleosis are reported occurring in previously healthy young men. All patients had positive heterophile reactions in a minimum dilution of 1:56 of unabsorbed serum and 1:28 after absorption with guinea pig kidney, characteristic hematologic findings and clinical manifestations seen in either acute pharyngitis or typhoid fever.

2. The clinical manifestations of mononucleosis were found to be far less variable than described in the literature. Practically all cases could be grouped into pharyngeal or typhoidal syndromes.

3. Lymphocytes usually constituted between 70 and 80 per cent of the leukocytes. One patient had 91 per cent lymphocytes. In four-fifths of the cases characteristic blood findings were present in the first week of illness; in the remainder they occurred during the second week of illness. The earliest appearance of characteristic blood changes was noted on the second day of illness; and the latest appearance occurred between the twelfth and fourteenth days of illness. The appearance of atypical lymphocytes paralleled the appearance of lymphocytosis. The duration of hematologic changes was usually one to two months. The shortest duration was two weeks and the longest was over three months.

4. Study of sedimentation rates revealed that three-quarters of patients with mononucleosis have normal sedimentation rates during the first week of illness; patients with markedly accelerated rates, especially in the first week of illness, are unlikely to have mononucleosis.

5. Positive heterophile reactions almost always appear during the first two weeks of illness; and if not present by that time, patients are unlikely to have mononucleosis. Highest titers are found usually during the second and third weeks of illness. Duration of the positive reaction is extremely variable. As a rule, positive reactions last four to eight weeks. The shortest duration was seven to nine days after onset of illness; one patient had a positive heterophile reaction seventy-two days after his illness began.

6. Reports of epidemics before the discovery of the heterophile antibody reaction cannot be

evaluated because it is uncertain whether the diseases described were actually mononucleosis. All epidemics reported since 1932 are characterized by relatively large numbers of subclinical cases and some by a paucity of positive heterophile reactions. None included guinea pig kidney absorption tests. It is suggested that these epidemics may possibly be instances of a disease, or diseases, related to but not identical with infectious mononucleosis, inasmuch as person to person transmission of mononucleosis is almost unknown and attempts at experimental transmissions have failed to reveal cases meeting adequate diagnostic criteria.[27]

7. It is proposed that reports of cases of mononucleosis be confined to patients meeting three diagnostic requisites: characteristic serologic, hematologic and clinical manifestations.

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Addendum: Since submission of manuscript, this series has increased to sixty-nine cases, typical in all respects.

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Infectious Mononucleosis*

The Value of Differential Absorption Tests in Its Serologic Diagnosis

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It is the purpose of this paper to emphasize the importance of performing absorption tests when the sheep cell agglutination test is utilized in an attempt to diagnose infectious mononucleosis. In an effort to establish greater acceptance of this practice the writer proposes, first, to emphasize the preëminent role which the sheep cell agglutination test occupies in making this diagnosis; second, to point out pitfalls in diagnosis that exist if the several types of heterophile antibodies are not differentiated by means of absorption tests; and third, to underscore how frequently it is helpful and necessary in the diagnosis of infectious mononucleosis to determine the character of the heterophile antibodies with absorption tests.

It is being generally recognized that laboratory tests are essential in establishing a diagnosis of infectious mononucleosis. The clinical picture alone will not permit a diagnosis with certainty because it may be mimicked by so many other entities.[1–8,91] There may be no clinical signs or symptoms.[1,4,6,9]

The hematologic features of infectious mononucleosis are sufficiently characteristic in most instances to be of extreme importance in *helping* to make the diagnosis but by themselves they are not specific[10–19] and are therefore useful only when judged in conjunction with all other clinical and laboratory findings. The cardinal hematologic features include a relative and absolute lymphocytosis plus the appearance of abnormal lymphocytes (virocytes[20]) in the peripheral blood. Numerous observers[4,16,20–35] have emphasized that the same features occur in other diseases, chiefly of viral origin (acute virus hepatitis, virus pneumonia, rubella, rubeola, roseola infantum, herpes zoster, herpes simplex (febrilis), influenza type B,[30] upper respiratory infections, undulant fever, rickettsialpox, allergic states). If there are any significant differences between the blood picture in infectious mononucleosis, on the one hand, and these other diseases, on the other, they are differences in degree: in infectious mononucleosis the lymphocytosis tends to be more extreme (even up to 90 per cent in occasional cases); the abnormal lymphocytes tend to occur in numbers considerably above 10 per cent and the abnormal lymphocytes tend to persist for longer periods of time (months or years).

In recent years there has been increasing evidence of hepatic involvement in infectious mononucleosis as judged clinically, chemically and histologically.[36–68,91] In the author's experience with a group of twenty-five sporadic cases[69] hepatic dysfunction was detected by blood chemical determinations in twenty-four of the cases (96 per cent). The author has been sufficiently impressed with the evidence that the liver is almost invariably involved in infectious mononucleosis to examine carefully the basis for the diagnosis in any case in which this evidence is lacking. However, although this finding is helpful in arriving at the final diagnosis, it is manifestly not specific for infectious mononucleosis. It is useful diagnostically chiefly in a negative sense; that is, its absence should make one question the validity of the diagnosis of infectious mononucleosis; its presence may still permit the diagnosis of numerous other diseases, even including several that frequently mimic the picture of infectious mononucleosis, such as acute virus hepatitis and virus pneumonia.

We are left, then, with the serologic test: the finding of sheep cell agglutinins. Ever since Paul and Bunnell[70] introduced the heterophile agglutination test as a diagnostic aid in infectious mononucleosis, and others[10,71–75] enhanced its applicability by means of differential absorption tests with guinea pig kidney and beef cell antigens, estimates have varied widely as to the

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extent of its specificity. If one judges by the percentages of positive serologic tests in twenty-one reported series totalling 1,643 cases, the extremes range from 50 to 100 per cent,[2,4–6,43,47,50,76–87,91,97] with the over-all average of approximately 83 per cent.

Such statistics are open to question for several reasons: (1) Interpretation of a positive test has varied widely in different reports because of the several technics employed, and has varied even when the technics employed have been similar. Definitions of a normal titer vary. It is also confusing that not all titers are expressed as the true dilution, that is, the *final* dilution. (2) Most workers have not attempted to confirm their agglutinations with absorption tests. (3) When the specificity of a serologic test is still under investigation, the basic diagnoses in the cases reported should be beyond question; but this is not possible because no specific clinical or laboratory yardstick is available. (4) If the investigator rigidly requires that all suspected cases yield positive serologic evidence before a diagnosis of infectious mononucleosis can be established, it follows that 100 per cent specificity will necessarily be obtained in any study.

Elsewhere[69] the writer has discussed in detail these and related factors which bear on this problem. For the purposes of the present communication these views will merely be summarized. Despite the questions already raised concerning the validity of statistics indicating an over-all average of 83 per cent specificity in a total of 1,643 reported cases, the writer has come to the conclusion that a more accurate evaluation of the percentage of specificity would be closer to 100 per cent. The chief reason for raising this figure, in his opinion, is the common reporting of "seronegative" cases on grounds that are open to criticism. Four factors contribute to this: (1) Failure to perform agglutination tests early enough in the illness; (2) failure to perform repeated agglutination tests late enough in the illness; (3) failure to perform confirmatory absorptions tests on serum with low titers and (4) failure to exclude cases simulating but not infectious mononucleosis.

Even if one accepts the premise that the sheep cell agglutination test possesses a high degree of specificity, the technic of its performance, and in particular the necessity for including confirmatory absorptions, remains an important consideration.

In approaching this problem three questions should first be answered: (1) *What are the results when the particular technic employed is applied to the serum of normal persons?* The writer, employing the technic of Davidsohn,[75] has examined the serum of 200 normal adults for heterophile antibodies and found no titer higher than 1:56.[92] The titer is expressed as the final titer *after* the addition of all diluents. These results confirm similar studies of Davidsohn[93] who examined the serum of 217 control persons, some of whom were healthy and some of whom had various diseases but no previous injection of horse serum. Davidsohn's technic in this study in 1933 differed from that of the writer only in that he (Davidsohn) incubated the tubes for two hours in a water bath at 37°c. and then overnight in the icebox; the author incubated the tubes at room temperature for two hours.

These studies agree well with the results obtained by Bernstein[2] in 300 hospital patients. Bernstein found a maximum titer of 1:80. He used a method similar to that originally described by Paul and Bunnell.[70]

Stuart and associates,[94] employing 0.5 per cent sheep cell suspension and incubation for two hours at 37.5°c., examined the serum from 300 normal persons or patients with diseases other than infectious mononucleosis. They found a titer of 1:80 or less in 99 per cent of their tests; 1:160 in 0.7 per cent and 1:320 in 0.3 per cent.

Barrett[95] examined the serum of 100 apparently healthy people, employing 0.5 per cent sheep cell suspension and incubating the tubes at room temperature prior to reading. The maximum titer was 1:20.

Bunnell[96] examined 1,600 sera from the Wassermann laboratory. When his results are converted into terms of final dilution, the titer was 1:64 or lower in 99.2 per cent of the specimens tested. A titer of 1:128 occurred in the remaining 0.8 per cent.

Butt and Foord[97] employed the same technic as Bunnell in examining the serum of 412 adult hospital patients. When their results are converted into terms of final dilution, the highest titer obtained was 1:64.

Smeall,[98] employing the technic of Paul and Bunnell, examined the serum of 765 patients not suffering from infectious mononucleosis or serum sickness. The highest titer obtained was 1:64.

To summarize: a titer of 1:56 may be considered the upper limit of normal in apparently healthy adult persons when examined by the

technic employed by the writer; that is, the technic of Davidsohn wherein the tubes are incubated at room temperature for two hours prior to reading. With the variations in technics indicated and with the varying methods of selecting "normal" persons for study, the upper limit of antibody titer has been found by other workers to be between 1:20 and 1:320.

2. *What are the results when the same technic is applied to the serum of patients with illnesses other than infectious mononucleosis?* The writer[92] has examined the serum of sixty-five patients with acute virus hepatitis (employing the same technic of Davidsohn[75] as noted above) and found an elevation above 1:56 in 20 per cent (thirteen patients) distributed as follows: 1:112 in eight cases, 1:224 in four cases and 1:448 in one case.

Kent[99] reported the case of a fourteen year old boy with leukemia with heterophile antibody titers of 1:4096 and 1:16384 (method of Paul and Bunnell). This patient died, was examined postmortem and was considered to be a case of myelocytic or monocytic leukemia.

Eaton, Murphy and Hanford[100] found no titers above 1:80 in fifty-six patients with atypical pneumonia; they found elevated titers of 1:160 "or higher" (exactly how much higher is not stated) in 8 per cent of 154 patients with post-vaccination hepatitis and in 13 per cent of sixty-eight patients with infectious hepatitis. When account is taken of the equal volume of sheep cells which these workers added to the serum dilutions, these titers as reported should be doubled. However, they employed the centrifuge technic and their elevated titers must be evaluated in the light of the knowledge that this method tends to yield higher titers than the sediment technic.[101–103]

Schultz[104] determined the heterophile antibody titers in a total of fifty-seven patients suffering from Hodgkin's disease and other sarcomas, blood dyscrasias or tuberculosis. She employed the technic of Davidsohn and read her tubes after overnight refrigeration (which tends to elevate the titers[94,95,102,105]). Forty-six of a total of 160 readings in these fifty-seven patients revealed titers above 1:56, the maximum being 1:448. These elevations were distributed among the following types of cases: Hodgkin's disease, agranulocytosis, monocytic leukemia, myelogenous leukemia, polycythemia, sarcoma other than Hodgkin's disease and tuberculosis.

Goldman, Fishkin and Peterson,[106] employing the technic of Stuart, determined the heterophile antibody reactions of 458 miscellaneous cases other than infectious mononucleosis and found titers of 1:80 or higher in forty-six cases. Fourteen had titers of 1:160 or higher (eleven with 1:160, two with 1:320 and one with 1:2560). They also examined the serum of twenty-nine persons with Hodgkin's disease and twenty-six with lymphomatous or leukemic states. Three of these fifty-five patients yielded titers of 1:80 and one had a titer of 1:160.

Carpenter, Kahler and Reilly[107] reported three instances of monocytic leukemia in which elevated heterophile antibody titers were recorded. The technic was not described. These titers were 1:512, 1:896 and 1:896, respectively.

To summarize: in disease states other than infectious mononucleosis (and serum sickness) heterophile antibody titers above normal levels are occasionally found. These are usually of the magnitude of 1:448 or lower but in four cases respective titers of 1:16384, 1:2560, 1:896 and 1:896 have been reported. The first patient was an instance of myelocytic or monocytic leukemia. The diagnosis of the second patient remains in doubt. The last two were cases of monocytic leukemia. The results of absorption studies, performed in the second, third and fourth cases, will be discussed below.

3. *Are the effects of the absorbing antigens (guinea pig kidney and beef erythrocytes) on the heterophile antibodies different in infectious mononucleosis from normal persons and from other disease states?*

Our knowledge of the effects of these antigens on the heterophile antibodies of infectious mononucleosis, serum disease and normal persons is primarily based upon reports published independently by three groups of workers[10,71–75] within several years after Paul and Bunnell (in January, 1932) noted the occurrence of heterophile antibodies in four cases of infectious mononucleosis. Earlier observations by Davidsohn[108,109] on the presence of heterophile antibodies in serum disease had stimulated Paul and Bunnell to undertake a similar study in rheumatic fever. During the course of this study in which they used various patients as controls, they accidentally found the highest titers in four patients with infectious mononucleosis.

The antisheep agglutinins in infectious mononucleosis are not of the Forssman type. They are not absorbed by a suspension of guinea pig kidney. The heterophile antibodies in serum disease and in normal persons are of the Forss-

man type and are readily absorbed by a suspension of guinea pig kidney. The agglutinins are promptly absorbed by boiled beef red corpuscles from the serum of patients with infectious mononucleosis and almost as well from the serum of patients with serum disease but not from normal serum. These characteristics may be tabulated as follows:

Type of Serum	Agglutinin Absorbed by	
	Boiled Beef Cells	Guinea Pig Kidney
Normal	No	Yes
Serum sickness	Yes	Yes
Infectious mononucleosis	Yes	No

These patterns have been repeatedly confirmed[44,69,79,81,89,92,95,101,102] but the point merits some elaboration. In the instance of normal sera, which are necessarily of low titer, the greatest percentages (95 to 98 per cent) will yield the pattern indicated, but in very rare instances patterns like that of serum sickness and infectious mononucleosis are obtained.[92,95] It is possible that these rare exceptions represent previously unrecognized cases of serum disease or infectious mononucleosis, but an equally plausible explanation is that because of the low magnitude of the titers involved the differentiation in rare cases is difficult. For example, if the unabsorbed titer is 1:7 or 1:14, and dilutions are prepared only down to 1:7 or even to 1:3.5, the distinction may be difficult should the beef cells absorb in one or even two tubes or should the guinea pig kidney absorb the agglutinins less than completely.

Furthermore, with regard to the statement that the absorption pattern in infectious mononucleosis has been observed repeatedly and stands confirmed, a question that may be properly raised is this: How can one confirm this serologic character when there is no absolute yardstick by which the basic diagnosis of the disease is indisputably established? These two statements are not incompatible. Repeatedly, as Paul and Bunnell originally observed, in patients whose clinical and/or other laboratory findings suggest the diagnosis of infectious mononucleosis, heterophile antibodies are found; with high degree of consistency these antibodies yield the absorption pattern described as characterizing infectious mononucleosis.[44,79,81,89,95,101,102] The writer is aware of no case of this type, with antibody titer above 1:896, in which this is not the absorption pattern. Similarly, even when the titer elevation above normal is less marked (for example 1:112, 1:224, or 1:448), the correlation between the likelihood of the diagnosis of infectious mononucleosis on clinical and/or laboratory grounds and the finding of an absorption pattern characteristic for infectious mononucleosis is high enough to encourage continued reliance on the use of the absorption test to establish this diagnosis.

This reasoning requires the recognition only of one further fact to establish the need to apply this differential test to suspected cases in which the antibody titer is within normal limits; namely, seemingly authentic cases of infectious mononucleosis are described in which during long periods of observation the titer does not exceed a level of 1:56 but the antibodies yield the characteristic infectious mononucleosis absorption pattern.[81,89,114,*] Furthermore, in some cases the agglutinins may be thus identified in the early days of illness at a low titer prior to their elevation to much higher titers. Moreover, as the serum is reëxamined repeatedly over a period of months, the titer may fall from exceedingly high levels to normal levels but still yield the infectious mononucleosis absorption pattern.[10,69,102] The *height* of the antibody titer alone, particularly when we are dealing with normal levels, or levels of moderate elevation up to 1:896, is not sufficient for prediction of the *type* of antibody present.

In regard to diseases other than infectious mononucleosis, exclusive of serum sickness:

1. Considerable data have been accumulated by applying the absorption tests to a variety of diseases. These include virus hepatitis, virus pneumonia, lymphomatous diseases, leukemia, polycythemia and tuberculosis.[44,89,90,92,100,104,106] In general it may be stated that, although a small percentage of these cases yields titers

* The writer has observed such a case recently. In addition he has repeatedly seen cases with high titers whose antibodies, abruptly or gradually, decrease to titers of 1:56 or 1:28 which still give the absorption characteristics of infectious mononucleosis antibodies; also, by retesting at frequent intervals he has observed such decreasing titers of infectious mononucleosis antibodies to change in absorption characteristics to normal antibodies without any further alteration in the titer itself.[69]

slightly above normal levels (usually no higher than 1:448), almost without exception these antibodies when absorbed prove to be normal antibodies; they seem to be the product of nonspecific stimulation of the normal heterophile antibodies.

2. In a very rare case exceptionally high antibody titers have been recorded. Four such cases have been observed, as previously pointed out. The first[99] of these, a fourteen year old boy with leukemia, had a titer of 1:16384 but his serum was not examined by means of absorptions. The author was uncertain whether these antibodies were "false positive" or due to a superimposed infectious mononucleosis. The second[106] of these was detected by screening 458 miscellaneous hospital patients. This patient had a titer of 1:2560. On absorption with guinea pig kidney the titer was reduced to 1:1280 (that is, suggestive of infectious mononucleosis). Unfortunately in this case no absorption with beef cells was carried out. The patient had had a recent admission to the hospital for trauma. The authors made no statement about any horse serum injection. They did say "there was nothing suggestive of infectious mononucleosis clinically or hematologically on either admission. The heterophile agglutination had been performed because of an atypical Wassermann reaction." The data are insufficient to allow any definite conclusions; the writer is left with the impression that this could well have been a case of infectious mononucleosis. The third and fourth patients[107] had monocytic leukemia. Each revealed a titer of 1:896. Absorptions were applied in both cases. In the first the antibodies were unmistakably of the normal type. In the second the results on the absorption were less clear: 1:28 after guinea pig kidney absorption and 1:14 after ox cell absorption. Although the authors interpreted this pattern as indicating normal antibodies, it is an equivocal result which is difficult to classify, probably resembling more closely the pattern of serum sickness. The patient whose monocytic leukemia was confirmed by necropsy examination had a long allergic background.

It is pertinent here to take note of the serologic findings described by Zarafonetis[88] in a patient with chronic myelogenous luekemia. When the sheep cell agglutinations were performed on the serum of this forty-year old female on six occasions over a period of forty-two days, the results were negative (less than 1:16) each time when the tubes were incubated for four hours at 37.5°C.; when the same tubes were further incubated overnight at 4°C., the reading in each test rose to 1:256; on further incubation for two hours at 37.5°C., the reading fell to 1:16 in the first five tests, to less than 1:16 in the sixth test. No absorption tests were done. Zarafonetis concluded that the serum of this patient had "cold agglutinins" for sheep cells up to a dilution of 1:256 and suggested that the "positive" heterophile agglutination tests ascribed to leukemia in the past are due to similar cold agglutinin effects. In the sheep cell agglutination tests on the three patients with leukemia cited above, the technic employed is stated only in the first case;[99] it was the technic of Paul and Bunnell[70] which includes overnight ice-box refrigeration. It is a reasonable possibility that the phenomenon described by Zarafonetis may have been operating in this instance. (It is of interest that Evans[116] tested the serum of fifty-six patients with infectious mononucleosis for the presence of cold hemagglutinins and found no titers higher than 1:32.)

To summarize: the heterophile antibodies in infectious mononucleosis yield a pattern on absorption which is different from that of the antibodies observed in normal persons and in other disease states. This infectious mononucleosis pattern is found with sufficient consistency in cases that otherwise are compatible with the diagnosis of infectious mononucleosis, and is absent with sufficient consistency in other disease states, that the test may be utilized with confidence.

The following case of infectious mononucleosis is presented to illustrate several of the diagnostic principles that have been discussed.

S. F., a twenty-eight year old engineer, was admitted to Beth Israel Hospital on November 7, 1950, with an illness which began five days previously with sore throat, fever (102–104°F.), loss of appetite, pains in the eyes and constipation. Four days before admission he complained of pains in the back of the neck and head; his neck felt stiff. Three days before admission he noted painful swellings on both sides of the neck and under the jaws. On this date he also began to experience "fluttering" pain intermittently along the anterior right lower ribs, unrelated to respirations; his urine appeared dark. All of these symptoms persisted until the time of admission. He was a non-smoker and had never been jaundiced.

Examination at the time of admission revealed a temperature of 102°F., pulse rate 112, respirations 24 and blood pressure 132/80. He appeared lethargic and acutely ill. No icterus was observed. Weakness of extraocular movements was noted. The skin was warm and dry but free

TABLE I
HEMATOLOGIC DATA IN CASE OF S. F.

Day of Illness	White Blood Cell Count (per cu. mm.)	Total Lymphocytes (per cent)	Abnormal Lymphocytes (per cent)	Sedimentation Rate (in mm./hour)
6	5,350	48	11	..
7	.....	54	13	20
10	6,600	54	many	..
12	8,800	86	many	35
14	11,800	88	many	..
20	21,450	91	many	51
26	9,200	40	?	16
36	.....	....	....	7
42	6,000	41	?	11
49	7,450	60.5	4.5	..

of an exanthem. The right tympanic membrane was injected. A mucoid nasal discharge was present. The pharynx was injected. The buccal mucosa bilaterally bore several pinpoint-sized, whitish vesicles near the molar teeth. The posterior neck muscles were tender and spastic. There was resistance to attempted flexion of the neck and rotation to the left. One left posterior cervical node and one right epitrochlear node were palpable and tender. The lungs were clear to percussion and auscultation. Examination of the heart was negative except for the tachycardia. The right lower ribs, anteriorly, were tender to percussion. The liver was not outlined but tenderness on palpation was elicited in the right upper abdomen. The tip of the spleen was palpated with some degree of uncertainty. The diagnostic impression was infectious mononucleosis or infectious hepatitis.

The white blood cell count at the time of admission was 5,350 with 48 per cent lymphocytes including 11 abnormal lymphocytes. (Table I.) On the second day in the hospital the peripheral blood smear showed 54 per cent lymphocytes with 13 per cent abnormal forms. The urine was free of bile and contained normal amounts of urobilinogen (0.4 Ehrlich units); otherwise it was also normal except for a faint trace of albumin. The stool appeared normal in color and consistency and contained bile pigment; no amebae were present. Spinal tap was performed this day. The fluid was under an initial pressure of 220 mm. of mercury; total protein was 54.5 mg. per cent; sugar was 87 mg. per cent; two cells were seen per cu. mm.; the Wassermann test, colloidal gold curve and culture were negative.

On this second hospital day the temperature remained elevated (up to 104.6°F.). The liver was palpable two fingerbreadths below the costal margin. It was exquisitely tender. The tip of the spleen was definitely palpable. The results of blood chemical examinations on this and subsequent days are listed in Table II. The sheep cell agglutination titer was "negative" (less than 1:50) on this same day. (Table III.)

During the first week in the hospital the temperature was of the septic type with upper extremes above 104°F. each day. The main complaints were pains in the back of the head, sore throat and stiffness of the neck. The abdominal and rib pains subsided. By the fifth day tender lymph nodes were palpable in the cervical, axillary, epitrochlear and inguinal areas, bilaterally. The liver decreased in size but the spleen remained palpable. On the seventh hospital day (twelfth day of illness), when the white blood cell count was 8,800, a lymphocytosis of 86 per cent was found, with many abnormal forms. Still the heterophile antibody titer on the ninth hospital day (fourteenth day of illness) was only 1:100. (Table III.) No absorptions were performed on these antibodies.

During the second week in the hospital the patient improved considerably. His temperature gradually fell to normal levels by the end of this week and thereafter during his seven and one-half weeks of hospitalization the temperature was normal except for four transient elevations between 100° and 101°F. The pains in the head were diminished by the third week in the hospital. His appetite improved after the tenth day and was almost ravenous one week later. The eyes were thought to be icteric on the sixteenth hospital day. The serum bilirubin was elevated to 2.3 mg. per cent at this period. The heterophile antibody titer on the sixteenth hospital day (twenty-first day of illness) was 1:112. This titer represented little change from that of the previous week, but absorption of the antibodies with guinea pig kidney and beef cell

antigen suspensions revealed infectious mononucleosis antibodies. (Table III.)

Thereafter, the patient's course was one of slow but continued improvement. He was jaundiced for just a few days. The adenopathy persisted for six weeks. The liver tenderness lasted several weeks, as did the splenomegaly. He was allowed out of bed at the end of the seventh week in the hospital and discharged in the eighth week, fifty-eight days after the onset of his illness.

The maximum heterophile antibody titer was 1:448 on the thirty-sixth and forty-second days of illness. The absorptions (Table III) for these two tests and for all others performed in the period of hospitalization yielded patterns characteristic for infectious mononucleosis, even on the two occasions when the titer was 1:56. When last repeated one week after discharge from the hospital, the titer was still slightly elevated (1:112) but absorptions now indicated normal Forssman antibodies. (Table III.)

TABLE II

RESULTS OF BLOOD CHEMICAL DETERMINATIONS IN CASE OF S. F.

Day of Illness	Bilirubin (mg. %)	Cephalin Flocculation (at 48 hr.)	Thymol Turbidity (units)	BSP: % Retention at 45′	Proteins (gm. %)		Alkaline Phosphatase (Bodansky units)	Prothrombin Activity	
					Albumin	Globulin		Sec.	% of Normal
7	1.7	Trace	8.5	6	5.1	2.0	2.8	15.9	27.5
13	0.7	4+	17.7	32	3.9	2.0	3.1	16.0	26.2
20	2.3	4+	26.0	12	4.5	2.5	4.4	15.5	29.5
29	2.3	4+	23.4	..	5.4	2.5	1.8	....	....
36	1.3	4+	29.6	..	4.9	2.5	1.9	14.9	>30
42	1.4	3–4+	16.9	..	4.9	2.1	3.3	15.8	28
48	1.2	3+	16.8	..	5.6	1.9	2.0	....	....
51	....	...	17.3	..	...	...	...	....	....
57	...	...	13.0	<5	...	...	...	....	....
65	1.3	4+	11.3	..	5.8	2.0	...	....	....

TABLE III*

SHEEP CELL AGGLUTINATION TESTS IN CASE OF S. F.

Day of Illness	Unabsorbed Titer	Titer after Absorption with	
		Guinea Pig Kidney	Ox Erythrocytes
7	<50†	.....	.....
14	100†	.....	.....
21	112	28	<14
29	112	56	< 3.5
34	56	28	< 3.5
36	448	224	14
42	448	112	7
48	112	28	7
57	56	28	7
65	112	<3.5	14

* Titers are expressed as reciprocal of actual titers.

† These first two tests were performed by the centrifuge technic of Straus;[11b] dilutions were prepared in multiples of 1:50; no absorptions were done. All other tests were by the sediment technic of Davidsohn.[15] In the test on the twenty-first day the dilutions were carried down to 1:14; in the subsequent tests, dilutions were carried down to 1:3.5.

The experience with this case emphasizes several points with respect to the diagnosis of infectious mononucleosis. First, even when the clinical picture, the hematologic data and the blood chemical determinations strongly suggest the diagnosis of infectious mononucleosis, serologic confirmation is still required to make the diagnosis absolute.

Second, in such a case, when the maximum elevation of the heterophile antibody titer remains within the limits that are occasionally observed in other diseases which enter into the differential diagnosis of infectious mononucleosis, a diagnostic distinction is readily feasible by means of the absorption tests. This distinction is possible early during the course of the illness when the titer of the heterophile antibodies shows little elevation above normal. Similarly, during the later weeks of the illness when the

antibody titer is declining, seemingly normal titers may reveal infectious mononucleosis antibodies when examined with absorbing antigens.

Third, when the antibody titer is declining during the period of convalescence, the height of the titer alone will not permit identification of the antibodies that are present. The reappearance of normal Forssman antibodies may occur at levels of titer that are little different from the declining titers which still evidenced infectious mononucleosis patterns. In fact, in this case the first titer in convalescence to yield a normal absorption pattern was higher (1:112) than the last previous titer which indicated infectious mononucleosis antibodies (1:56).

Perhaps the most significant point to be derived from this case is that without the use of absorption tests it would not have been possible to state that the heterophile antibody test was positive for infectious mononucleosis. The validity of this statement will be readily recognized when it is recalled that titers up to 1:448 have been reported occasionally in cases other than infectious mononucleosis but that these usually prove to be normal antibodies when screened with the absorptions.

What this case cannot illustrate is the equal necessity for supplementing the agglutination test with absorptions when the titer is higher than 1:448. (Until recently the writer used to believe, on the basis of his own experience, that a titer of 1:896 or higher hardly required corroboration by means of absorptions for practical purposes, when absorption tests were not feasible, and in the absence of suspicion of serum sickness. This view has been modified for the reasons which follow.) The recent report[107] of two cases of monocytic leukemia with titers of 1:896, in at least one of which the absorptions indicated normal (Forssman) antibodies, has lifted to 1:896 the level of titer to which normal antibodies have been proved to rise. The distinction in such circumstances can be made only by absorbing the antibodies. Admittedly, this experience is a rare one but if allowance is made for its possible recurrence one must examine by absorption tests all heterophile antibodies at titers up to 1:896. The report by Kent[99] of the finding of a titer of 1:16384 in a case of leukemia confuses the situation somewhat. In the absence of examination of these antibodies by absorptions it is impossible to state what type of antibodies they were. The possibility that a cold-agglutinin effect was operating has already been pointed out. Until others report similar high titers in cases other than infectious mononucleosis and identify the antibodies by means of absorption tests, final decision in this matter must be deferred. For the present, titers up to 1:896 should be screened with absorptions. Titers higher than 1:896 must be evaluated cautiously in the light of other data in the case. If absorptions have been previously accomplished in such a case at lower levels of titer and infectious mononucleosis antibodies have been revealed, it will not be necessary to absorb at these higher titers. If, however, with or without the benefit of previous absorptions, the diagnosis of infectious mononucleosis is still in doubt, such an elevated titer may be considered presumptive evidence of infectious mononucleosis.

Even conceding, under the circumstances described, that a titer of 1:1792 or higher may be accepted for practical purposes as presumptive evidence of infectious mononucleosis, there still exists an important reason why the serum of such a patient should be examined by absorption technic. A considerable period of time (weeks and even months) may elapse during the illness of a patient with infectious mononucleosis before the heterophile antibodies rise to such levels. For example, the writer, with Bakst, recently described such a case[110] in which the antibodies first rose to a titer of 1:1792 on the forty-seventh day of illness. In this particular case the difficult differentiation between Hodgkin's disease and infectious mononucleosis was of great clinical importance. Other cases have been noted in which elevated antibody titers did not appear till the second and even the third month of illness.[51,66,81,84,111–114] Therefore, if the antibodies are repeatedly absorbed in such cases in the weeks preceding a rise to such seemingly significant levels, the diagnosis of infectious mononucleosis may be established much sooner.

It should also be remembered that many cases of infectious mononucleosis never attain very high titers. In the writer's study of twenty-five cases[69] three had maximum titers of 1:448, five cases had maximum titers of 1:896 and the remaining seventeen showed maximum titers of 1:1792 and above. Thus approximately one-third of this series of cases required absorption tests for the diagnosis at all times during observed periods of their illness.

Moreover, even in the face of titers of 1:1792 and above, confirmation by absorption is desirable (if not previously obtained) whenever

(1) the possibility of another disease with ominous prognosis enters into consideration; or (2) the case serves as part of a study on the subject of infectious mononucleosis.

SUMMARY

1. The sheep cell agglutination test is preëminent in the diagnosis of infectious mononucleosis.

2. Absorptions with guinea pig kidney and beef cell antigen suspensions, greatly enhance the specificity of the sheep cell agglutination test in the diagnosis of infectious mononucleosis.

3. The use of the absorption tests as part of the examination of serum for heterophile antibodies is routinely indicated whenever the antibody titer is 1:896 or lower. This indication rests on the reported identification of normal Forssman antibodies in diseases other than infectious mononucleosis at titers up to this level.

4. In the absence of suspicion of serum sickness a titer of 1:1792 or higher may, for practical purposes, be presumed to be diagnostic of infectious mononucleosis. Absorption of the antibodies at any titer is necessary to differentiate serum sickness antibodies from those of infectious mononucleosis.

5. Under certain special circumstances absorption tests should be employed even in cases which reveal titers of 1:1792 or higher.

Addendum: Since this manuscript was submitted for publication, Southam, Goldsmith and Burchenal[117] encountered heterophile antibody titers above 1:56 in 16 per cent of 187 cases of leukemia and other neoplastic diseases, the highest titer being 1:896 in a case of acute leukemia. However, they identified these antibodies as normal Forssman antibodies by means of absorption tests. Davidsohn, Stern and Kashiwagi[118] make the point that the presumptive (unabsorbed) heterophile antibody test is entirely non-specific but that the differential test is sensitive and specific for infectious mononucleosis.

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Review

Clinical-chemical Studies of Acid-base Abnormalities*

Changes in Acid-base Balance Observed in Renal and Respiratory Disease

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LABORATORY and clinical investigation in the past fifty years has provided a knowledge of disturbances in acid-base balance of the blood which often is indispensable for accurate appraisal and treatment of many clinical conditions. A review of the literature defining the theoretic concepts of acid-base balance and their practical application to clinical medicine has been accomplished by Peters and Van Slyke.[1] Comprehension of the electrolyte pattern of serum and extracellular fluid, of its regulation and of the changes which take place in clinical acid-base abnormalities has been advanced by the studies of Gamble[2] and his associates. Recent papers by Singer and Hastings,[3] and Singer[4] have stressed the necessity for consideration of the whole blood buffer systems in dealing with clinical problems of acid-base balance and have emphasized the fact that errors in diagnosis or treatment may occur when a single datum concerned with acid-base disturbance, such as CO_2 content or CO_2 combining power of blood, is the only known datum. They have again defined the principal factors necessary for adequate knowledge of acid-base balance of the blood and developed nomograms which afford the clinician practical means for diagnosis and treatment of acid-base abnormalities.

The purpose of this paper is to record investigations of acid-base balance of the blood in several patients with renal disease and respiratory disease. Emphasis has been placed on a consideration of the changes in the whole blood buffer base which occur during treatment. The attempt has been made to define quantitatively the functions of various components of the buffer base. Acid-base abnormalities in relation to intracellular and extracellular ionic patterns are described. Furthermore, the data are considered from the point of view of their clinical application to the treatment of two common disease states.

For the purpose of presentation this paper is divided into three parts. Part I deals with theoretic considerations of acid-base balance of the blood in order to clarify the interpretation of the data subsequently presented. Part II sets forth the clinical and chemical data on individual cases with abbreviated comment. Part III includes examples of intracellular and extracellular ionic patterns derived from the data on several patients. The Appendix includes the methods, tables of chemical values and calculations used in these investigations.

PART I

Table I defines factors and symbols used throughout this paper. The definition of buffer base (B_B^+) is that of Singer and Hastings[3] and includes "the base or cation equivalent to the sum total of the buffer anions," i.e., bicarbonate, hemoglobin, serum protein and inorganic phosphate. The buffer anions and that moiety of

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base bound to them are considered as the metabolic component in the regulation of acid-base balance of the blood. The respiratory component in acid-base balance of the blood is concerned with the bicarbonate-carbonic acid system. It will be recalled that the Henderson-Hasselbalch equation defines the relation of the bicarbonate-carbonic acid components of serum in terms of pH:

$$pH_s = pK_s + \log \frac{(HCO_3^-)_s}{(H_2CO_3)_s}$$

$$pH = pK + \log \frac{(CO_2)_s - f_s \cdot P_{CO_2}}{f_s \cdot P_{CO_2}}$$

The concentration of $(H_2CO_3)_s$ varies directly with the partial pressure of CO_2, (P_{CO_2}), and equals a constant, f_s, times P_{CO_2}. The values for the constants pK_s and f_s are 6.10,[5] and 0.0301,[6] respectively. Substituting in the foregoing equations one obtains:

$$pH_s = pK_s + \log \frac{(CO_2)_s - 0.0301\ P_{CO_2}}{0.0301\ P_{CO_2}}$$

Ventilatory and respiratory functions control the P_{CO_2} of arterial blood since it is in approximate equilibrium with the partial pressure of CO_2 in the lung alveoli. Changes in pulmonary function which affect the partial pressure of alveolar CO_2, and consequently $(H_2CO_3)_s$, therefore may affect the pH.

The relation of the buffer base and P_{CO_2} to the total cation-anion concentration of whole blood is important. It will be recalled that since buffer base may be expressed as follows[3]

$$B_B^+ = (B^+) - (A^-)$$

variations in either (B^+) or (A^-), or both, will have a direct effect on (B_B^+). The detailed relation of the buffer base and P_{CO_2} to the total cation-anion concentration of the blood will be brought out in the data to be presented.

Hypothetic Acid-base Disturbances. In an effort to represent the data in this paper in a simplified form the various nomograms[3,4,7,8] proposed previously have not been employed. Instead, the whole blood buffer base $(B_B^+)_b$, representing the metabolic component, and P_{CO_2}, representing the respiratory component concerned with regulation of the blood pH, have been depicted graphically by vertical blocks in Figure 1 and the corresponding data in Table II. This figure shows hypothetic variations in blood buffer base and P_{CO_2} with resulting effects on pH. For illus-

TABLE I
DEFINITIONS OF FACTORS AND SYMBOLS
(MODIFIED FROM SINGER AND HASTINGS[3])

Factor	Symbol*	Definition
Volumes per cent	Vols. %	Volumes of dry gas measured at 0°C. and 760 mm. pressure per 100 volumes of solution; a common unit for expressing CO_2 or O_2 or bicarbonate content of blood but less desirable than the unit of mM/L.
Millimol per liter	mM/L.	$\frac{1}{1000}$ gm. M of a substance per liter of solution. CO_2, mM/L. $= (0.45)(CO_2$, vols. %)
Milliequivalent per liter	mEq./L.	$\frac{1}{1000}$ gm. equivalent of an ion per liter of solution. X^-, mEq./L. = (X, mM/L.) × (valence of X^-)
CO_2 tension	P_{CO_2}	CO_2 pressure; pressure of dry gas, in mm. of Hg, with which the dissolved carbonic acid is in equilibrium
Carbonic acid content	(H_2CO_3)	Concentration of H_2CO_3 mM/L. $= f \cdot P_{CO_2}$
CO_2 content	(CO_2)	Concentration of total CO_2 in solution
Bicarbonate	(HCO_3^-)	Bicarbonate concentration, mEq./L.; in this paper carbamino CO_2 is included in bicarbonate $(HCO_3^-) = (CO_2) - f \cdot P_{CO_2}$
Base	B^+	Any cation in biologic fluids; (this biochemical usage is counter to the modern physicochemical definition of base)
Total base	(B^+)	Sum, in mEq./L., of concentrations of individual cations in serum
Buffer base	(B_B^+)	Base equivalent to the sum of buffer anion concentrations (including HCO_3^-) in mEq./L.
Fixed acid	(A^-)	Sum, in mEq./L., of concentrations of individual non-buffer anions
Oxygen capacity	O_2 cap.	The total amount of oxygen carried by the blood, expressed as vols. %
Oxygen content	O_2 cont.	The oxygen content of the blood, expressed as vols. %
Protein anions	Pr^-	The serum proteins expressed as the mEq. of anions equivalent to their base-binding capacity
Buffer base bound by serum proteins and phosphate	P^-	The portion of the total buffer base bound by the serum proteins plus phosphate
Anion equivalency of hemoglobin	(Hb_t^-)	The anion equivalency of the total hemoglobin; the sum of the anion equivalency of the oxygenated hemoglobin (HbO_2) and the reduced hemoglobin (Hb^-)
Base bound by Hb, HCO_3, etc.	$B^+(HCO_3^-)$, etc.	The milliequivalents of base bound by the given concentration of hemoglobin, bicarbonate, etc.
Undetermined anions	(X^-)	The undetermined anions of the serum or cells
Hematocrit	Vc	Volume fraction of packed red cells in whole blood

* Subscript "s" denotes plasma or serum, subscript "c" denotes red cells and subscript "b" denotes whole blood.

trative purposes the values have been exaggerated to portray examples of "metabolic alkalosis" and "acidosis" and "respiratory alkalosis" and "acidosis" in which changes have occurred in only one of the primary variables. Actually, a change in one independent variable, for example (B_B^+), is almost always accompanied with change in the other independent variable, (P_{CO_2}), unless the primary disturbance is of short duration. This is especially true in the case of primary metabolic disturbances. Deviations in blood buffer base and CO_2 pressure may be termed "mixed" disturbances in that both metabolic and respiratory mechanisms are involved. However, definition as to which disturbance is the primary one will rest on additional chemical data and precise clinical evaluation. The last column in Figure 1 is an example of deviation in both the blood buffer base and the P_{CO_2} in which the primary disturbance was "metabolic." Throughout this paper deviation in both respiratory and metabolic components is designated "mixed disturbances."

In this study normal values for arterial pH are considered to range from 7.36 to 7.46.[3] While shifts of pH within this range may be significant in relation to treatment, we have not accepted a situation as one of acidosis or alkalosis unless pH values were found outside these limits.

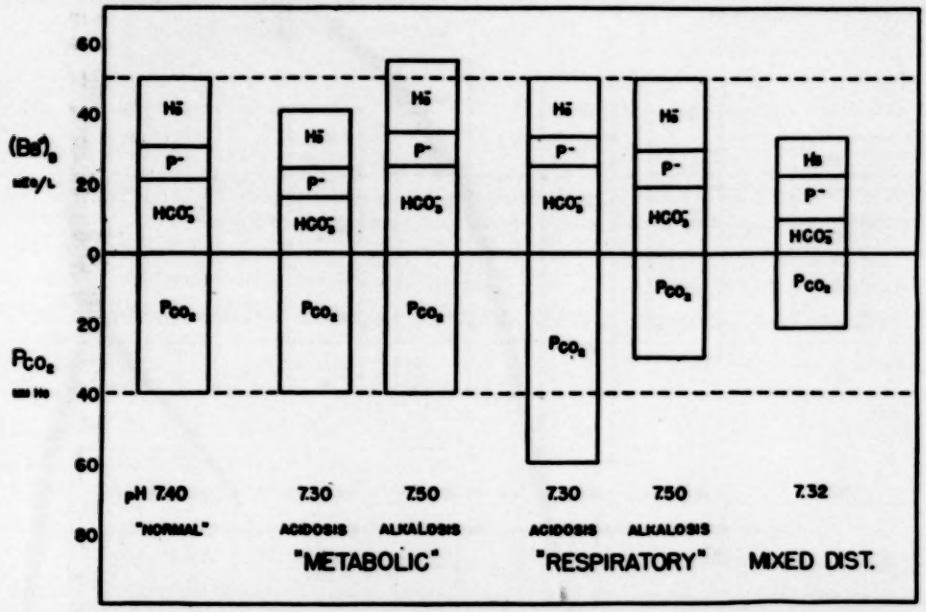

FIG. 1. Hypothetic changes in the blood buffer base, HCO_3, and pH in metabolic and respiratory disturbances. In this and subsequent figures, 3 to 7, H_B^- represents the base bound by hemoglobin at a given pH, saturation and concentration of hemoglobin. P^- is the amount of base combined with phosphate and protein. The value for P^- is further dependent, to a minor extent, upon the concentration of serum albumin and globulin and the pH. The HCO_3^- is the amount of base bound by bicarbonate. All values are expressed as mEq. per L. of whole blood. (See Table II.) Metabolic disturbances are represented as having a "normal" fixed P_{CO_2} with a varying blood buffer base, $(B_B^+)_b$, and pH. Respiratory disturbances are represented as having a "normal" fixed $(B_B^+)_b$ with a varying P_{CO_2} and pH. For simplicity, the hemoglobin concentration has been assumed to be 15 gm. per cent and the oxygenation of the blood 95 per cent. The mixed disturbance data have been taken from Case I.

PART II

The six cases to be presented in this paper include three patients with primary renal insufficiency, one patient with hypertensive cardiovascular renal disease, one patient with extensive pulmonary fibrosis and emphysema and cor pulmonale, and one patient with severe bronchial asthma, pulmonary fibrosis and emphysema. Salient features of the medical history, routine laboratory data and hospital course have been outlined, together with a brief summary of the data on acid-base balance studies for each case. An extensive consideration of the data is to be found under Remarks. Figures 2 to 7 and Tables III and IV graphically portray and record the data in the six cases.

TABLE II

DATA USED FOR DISTRIBUTION OF BLOOD BUFFER BASE IN FIGURE 1*

	pH	Vc	$B^+(HCO_3^-)_b$ mEq./L.	$B^+(P^-)_b$ mEq./L.	$B^+(Hb_t^-)_b$ mEq./L.	$(B_B^+)_b$ mEq./L.	P_{CO_2} mm. Hg
"Normal"	7.40	.45	20.7	10.6	18.6	50.0	40.0
"Metabolic" acidosis	7.30	.45	15.8	8.5	16.5	41.0	40.0
"Metabolic" alkalosis	7.50	.45	24.8	9.4	20.6	55.0	40.0
"Respiratory" acidosis	7.30	.45	24.3	9.2	16.5	50.0	60.0
"Respiratory" alkalosis	7.50	.45	18.6	10.6	20.6	50.0	30.0
Mixed disturbance	7.32	.33	9.5	12.7	10.6	33.0	21.5

* Quantitative data used for graphic presentation of acid-base disturbances, Figure 1. Normal values taken from references 3, 9 and 10. For explanation of symbols see Table I and legend to Figure 1.

TABLE III

DISTRIBUTION OF BLOOD BUFFER BASE IN PATIENTS WITH RENAL DISEASE*

	Date	pH (1)	Vc (2)	$B^+(HCO_3^-)_b$ (3) mEq./L.	$B^+(Pr^-)_b$ (4) mEq./L.	$B^+(HPO_4^=)_b$ (5) mEq./L.	$B^+(P^-)_b$ (6) mEq./L.	$B^+(Hb_t^-)_b$ (7) mEq./L.	$(B_B^+)_b$ (8) mEq./L.	P_{CO_2} (9) mm. Hg
"Normal"	.....	7.40	.45	20.7	8.6	2.0	10.6	18.6	50.0	40.0
Case No.										
	11/29/50	7.32	.33	9.5	10.3	3.5	13.8	9.7	33.0	21.5
I	12/4	7.50	.34	21.4	8.4	3.5	11.9	16.4	49.7	32.0
	12/8	7.52	.39	21.7	7.9	2.3	10.2	18.8	50.7	33.0
	1/8/51	7.33	.31	11.2	10.6	4.7	15.3	7.5	34.0	24.0
	1/12	7.42	.29	16.1	10.2	4.2	14.4	9.5	40.0	29.0
II	1/15	7.41	.34	19.2	10.0	4.3	14.3	11.5	45.0	35.0
	2/9	7.41	.29	13.3	11.9	5.8	17.7	7.0	38.0	24.0
	2/21	7.40	.32	18.2	10.6	5.5	16.1	9.7	44.0	34.0
	11/1/50	7.37	.35	15.0	4.4	3.9	8.3	16.7	40.0	31.0
	11/6	7.41	.32	15.7	5.0	4.5	9.5	14.2	39.4	29.0
III	11/8	7.45	.27	18.8	6.9	2.9	9.8	13.7	42.3	30.0
	11/10	7.45	.33	24.3	6.0	2.2	8.2	17.5	50.0	41.0
	11/13	7.44	.33	22.6	6.4	2.3	8.7	16.1	47.4	39.0
	3/10/50	7.36	.13	17.2	10.2	2.4	12.6	6.9	36.7	34.0
	3/11	7.40	.15	16.7	....	...	....	....	37.8	29.0
	3/15	7.38	.19	16.8	....	3.4	....	....	38.0	31.0
	3/27	7.33	.27	13.3	9.8	4.1	13.9	7.8	35.0	28.5
I	4/4	7.35	.29	11.5	....	...	....	....	35.0	24.0
V	4/7	7.37	.25	17.6	10.1	3.4	13.5	8.9	40.0	34.0
	4/10	7.36	.24	16.9	9.6	2.9	12.5	9.6	39.0	34.0
	7/10	7.37	.30	12.1	....	...	....	....	35.6	24.0
	7/12	7.38	.34	11.1	10.5	3.6	14.1	10.8	36.0	22.6
	12/27	7.38	.32	12.5	9.0	3.5	12.5	12.0	37.0	25.0
	1/3/51	7.38	.35	18.8	8.5	3.2	11.7	13.5	44.0	37.0

* This table lists the data used to construct Figures 2 to 5. Data in columns 1 and 2 were directly determined. Data in columns 8 and 9 were derived from the nomogram of Singer and Hastings.[3] The data in column 7 are derived by subtracting the sum of columns 3, 4 and 5 from 8. Column 6 is the sum of columns 4 and 5. All buffer values are expressed as mEq./L. of whole blood. "Normal" values taken from references 3, 9 and 10.

CASE I. A seventy-two year old white male (Hospital No. 27,421) was admitted for the fifth time on November 10, 1950, because of progressive shortness of breath, ankle swelling, chest pain and palpitation for two months. In 1949 the diagnosis of hypertensive cardiovascular disease with mild cardiac and renal insufficiency was made. At that time the blood pressure was 210/105; the blood non-protein nitrogen was elevated to 77 mg. per cent. In May, 1950, digitalis was required to relieve cardiac failure. The blood non-protein nitrogen had risen to 126 mg. per cent; the PSP excretion was 20 per cent in two hours.

On the final admission the patient appeared malnourished and dyspneic with rapid shallow respirations. Cyanosis and edema were absent. The temperature was normal; the blood pressure was 170/118; the weight was 104 pounds. The heart was enlarged to percussion; a forceful apex impulse was seen and felt in the anterior axillary line in the sixth interspace. The lungs were clear to percussion and auscultation. The remainder of the physical examination was not remarkable. The admission laboratory data revealed a red blood cell count of 2,570,000 with 8.5 gm. of hemoglobin present. The blood sedimentation rate (Westergren) was 48 mm./hour. The urine specific gravity was 1.021 with 2+ albumin and negative sediment. Admission electrocardiogram showed evidence of left ventricular hypertrophy with myocardial damage. Roentgenogram and fluoroscopy of the chest revealed enlargement of the cardiac silhouette with calcification of the aorta.

The patient received a 440 mg. sodium diet, maintenance dosage of digitalis leaf and transfusions of citrated blood. However, he responded poorly to therapy and his hospital course was one of gradual deterioration with rising blood non-protein nitrogen and periods of mental confusion, nausea and anorexia. Serial electrocardiograms showed progressive changes with prolongation of Q-T interval and delayed interventricular conduction. Signs of sacral edema appeared on December 9th together with moist rales at the left lung base and congested neck veins. However, respiratory rate did not increase above 24 per minute until December 11th. Coma and signs of increasing pulmonary congestion then developed and the patient expired. Postmortem findings showed cardiac hypertrophy with severe coronary sclerosis, an old myocardial infarct, bilateral bronchopneumonia with chronic passive congestion of the lungs, hydrothorax and acute and chronic pyelonephritis.

Acid-base balance studies of the blood on this patient on November 29th showed a significant diminution in buffer base to 33 mEq./L. (Fig. 2, Table III.) This reduction of buffer base was due

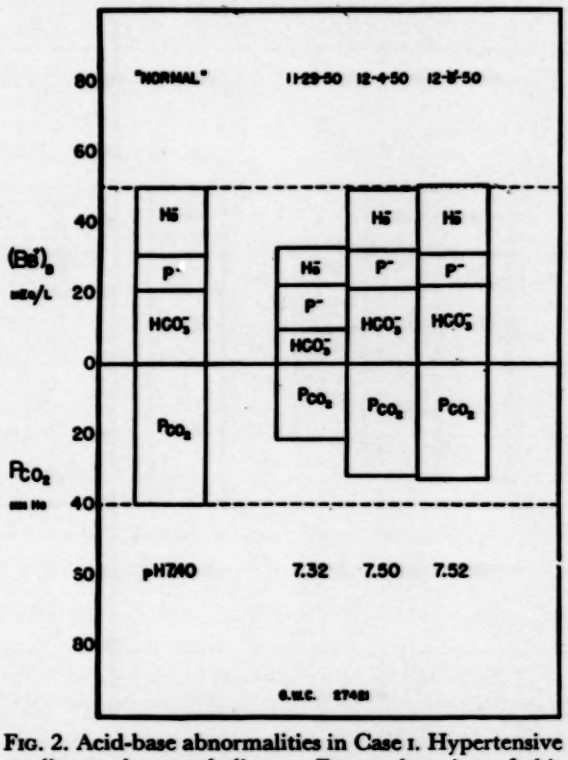

FIG. 2. Acid-base abnormalities in Case I. Hypertensive cardiovasçular renal disease. For explanation of this and subsequent figures, 3 to 7, see text.

to lowering of hemoglobin and bicarbonate components of the buffer systems. Acidosis was present with a pH value of 7.32. P_{CO_2} was also much reduced. The primary disturbance was "metabolic," a fixed base deficit. (Table VI.) The administration of large amounts of sodium lactate between November 30th and December 4th was associated with a return of the buffer base to normal values; however, the patient became alkalotic, pH 7.50 to 7.52. Arterial oxygen unsaturation was present. CO_2 pressure had risen but not to normal values. Concomitant serum electrolyte studies in this patient showed a persistent base deficit, $(B^+)_e$, but no abnormal increase in fixed acids, $(A^-)_e$, (non-buffer anions composed of $(Cl^-)_e$ and $(X^-)_e$). Regression of $(Cl^-)_e$ accompanied the large increase in $(HCO_3^-)_e$ with final significant reduction in $(A^-)_e$.

In summary, acid-base abnormalities found were first a "mixed disturbance," a primary

"metabolic acidosis" with secondary "respiratory alkalosis" and an abnormally low pH, which under treatment changed to a primary "respiratory alkalosis," with an abnormally high pH.

the day following admission. With the administration of transfusions and sodium bicarbonate by mouth the patient's symptoms disappeared rapidly. He was discharged January 15th much improved symptomatically, with the recommendation to continue sodium bicarbonate, 10 gm. daily.

TABLE IV

DISTRIBUTION OF BLOOD BUFFER BASE IN PATIENTS WITH RESPIRATORY DISEASE*

	Date	pH (1)	Vc (2)	$B^+(HCO_3^-)_b$ (3) mEq./L.	$B^+(Pr^-)_b$ (4) mEq./L.	$B^+(HPO_4^=)_b$ (5) mEq./L.	$B^+(P^-)_b$ (6) mEq./L.	$B^+(Hb_t^-)_b$ (7) mEq./L.	$(B_B^+)_b$ (8) mEq./L.	P_{CO_2} (9) mm. Hg
"Normal"	.....	7.40	.45	20.7	8.6	2.0	10.6	18.6	50.0	40.0
Case No.										
	2/7/51	7.41	.43	30.0	9.3	1.6	10.9	16.4	57.3	58.0
V	2/12	7.39	.50	36.9	8.1	1.7	9.8	19.3	66.0	76.0
	2/26	7.47	.45	29.3	8.9	2.1	11.0	17.7	58.0	52.0
	7/3/50	7.42	.35	39.6	...	...	26.9		66.5	74.0
	7/6	7.52	.34	26.8	...	...	27.0		53.8	38.0
VI	7/7	7.48	.33	27.9	...	...	28.1		56.0	44.0
	11/14	7.42	.42	26.7	...	...	27.2		53.9	49.0
	11/15	7.39	.43	26.8	...	...	27.2		54.0	56.0
	11/16	7.38	.41	28.4	...	...	27.0		55.4	59.0
	11/17	7.36	.40	28.7	9.7	2.4	12.1	14.2	55.0	62.0

* Data used for construction of Figures 6 and 7. For derivation see Table III. In Case VI the values for base bound by hemoglobin, protein and phosphorus were obtained by subtracting the base bound by bicarbonate from the whole blood buffer base.

CASE II. A forty-three year old postmaster (Hospital No. 27,874), followed up by this hospital for three years, entered on January 4, 1951, because of weakness, nausea, vomiting and severe leg cramps. Diagnosis of polycystic kidney disease was made in 1945 while in the Army. In 1948 investigation here revealed hypertension, large nodular kidneys and elevated blood non-protein nitrogen. Frequent follow-up studies showed evidence of rapid progression of renal insufficiency during 1950.

Physical examination revealed normal mental status, pallor, blood pressure of 140/110, protuberant abdomen with large masses in each flank, normal-sized heart and no edema. Initial laboratory studies showed a hemoglobin of 9.1 gm. per cent and a red cell count of 2,400,000. Urinalysis revealed a trace of albumin, a specific gravity of 1.008 and rare red and white cells in the centrifuged sediment. The blood non-protein nitrogen was 192 mg. per cent. The patient was given a diet as tolerated, without salt restriction, and 500 ml. of citrated blood

The patient returned on February 8th because of aching pain in the left flank and recurrence of mild muscle cramps, weakness and nausea. On admission the left kidney appeared larger than previously noted and was markedly tender. The day following admission the patient voided bloody urine containing clots. Thereafter pain and hematuria gradually subsided. Measures directed toward correcting the buffer deficit found on the second admission were gratifying and the patient left the hospital February 21st symptomatically improved, with recommendation to continue taking sodium bicarbonate and return for further transfusions. At no time were respiratory disturbances indicative of acidosis noted in this patient.

Acid-base balance data are shown in Figure 3 and Table III. The primary disturbance in acid-base balance was a severe loss of buffer base attributable to low hemoglobin and bicarbonate values. These findings, together with a low

blood pH, indicated a state of metabolic acidosis. The buffer fraction, P^-, was increased due to an increase in phosphate and to more plasma per liter of blood, i.e., a low hematocrit. Attempts to correct the deficit in buffer base by transfusion and administration of sodium bicarbonate were quite successful.

On the second admission acid-base studies again showed a buffer base deficit due to diminution in hemoglobin and bicarbonate. Blood pH, however, was normal.

Electrolyte patterns in the serum of this patient showed a diminution in total base, $(B^+)_s$, and a slight elevation of fixed acids, $(A^-)_s$, on the first admission. The undetermined acids, $(X^-)_s$, were considerably increased. On the first admission under treatment $(B^+)_s$ and $(HCO_3^-)_s$ rose and $(A^-)_s$ decreased due to regression of $(Cl^-)_s$. On the second admission similar changes occurred although of less degree. The electrolyte pattern in this patient revealed mild acid excess which was corrected and a slight base deficit.

Acid-base abnormalities in this case may be summarized as an initial "mixed disturbance," primary "metabolic acidosis" with secondary "respiratory alkalosis" and an abnormally low pH which were corrected by therapy.

Case III. A twenty-six year old male mill worker (Hospital No. 27,095) was readmitted October 8, 1950, because of recurrent diarrhea.

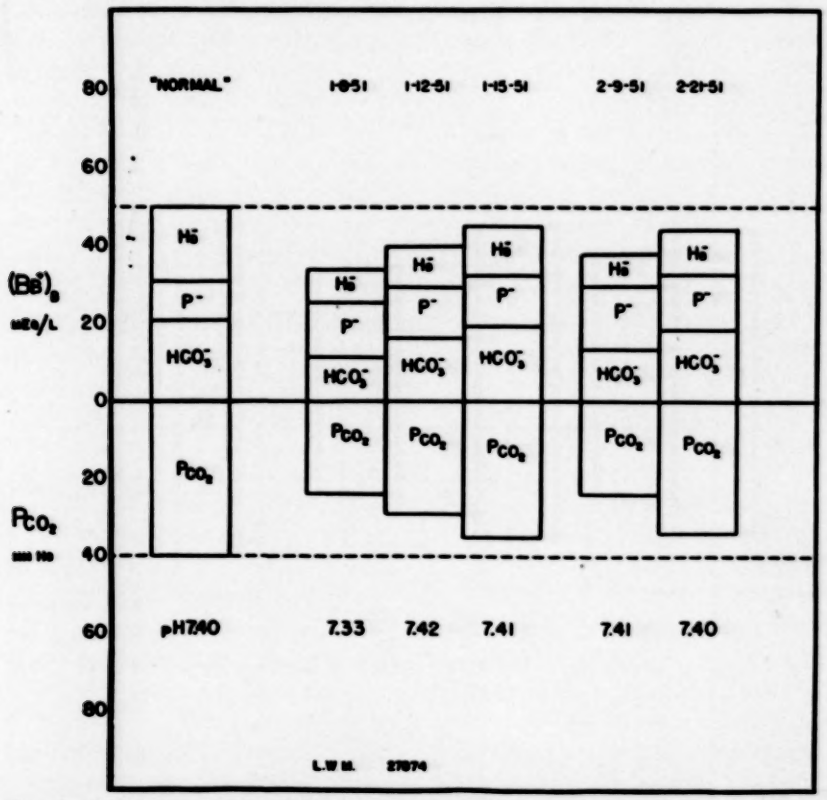

Fig. 3. Acid-base abnormalities in Case II. Polycystic kidney disease; uremia.

In 1949 the diagnosis of Hodgkin's disease with mediastinal adenopathy was made at this hospital and he was given x-ray therapy with objective and subjective improvement. He was readmitted in April, 1950, because of weight loss and diarrhea. While hospitalized it was noted that he had severe albuminuria, 8 to 10 gm./24 hours, and hypoproteinemia. Massive edema developed. Later spontaneous diuresis occurred. X-ray therapy of the dorsal and lumbar spine was followed with cessation of diarrhea. He was discharged June 22, 1950, much improved. However, three weeks before present admission watery diarrhea with blood streaking recurred; the patient lost weight and strength.

Admission physical examination revealed a blood pressure of 110/60, a normal oral temperature, pulse 76 beats/minute, pallor, ema-

ciation, small cervical lymph nodes, a palpable tender liver and no edema.

The hemoglobin was 9.2 gm. per cent and the red cell count 3,630,000. The urine contained 2+, 3+ albumin; the specific gravity was 1.021. There were many granular casts in the sediment. The blood non-protein nitrogen was 38 mg. per cent.

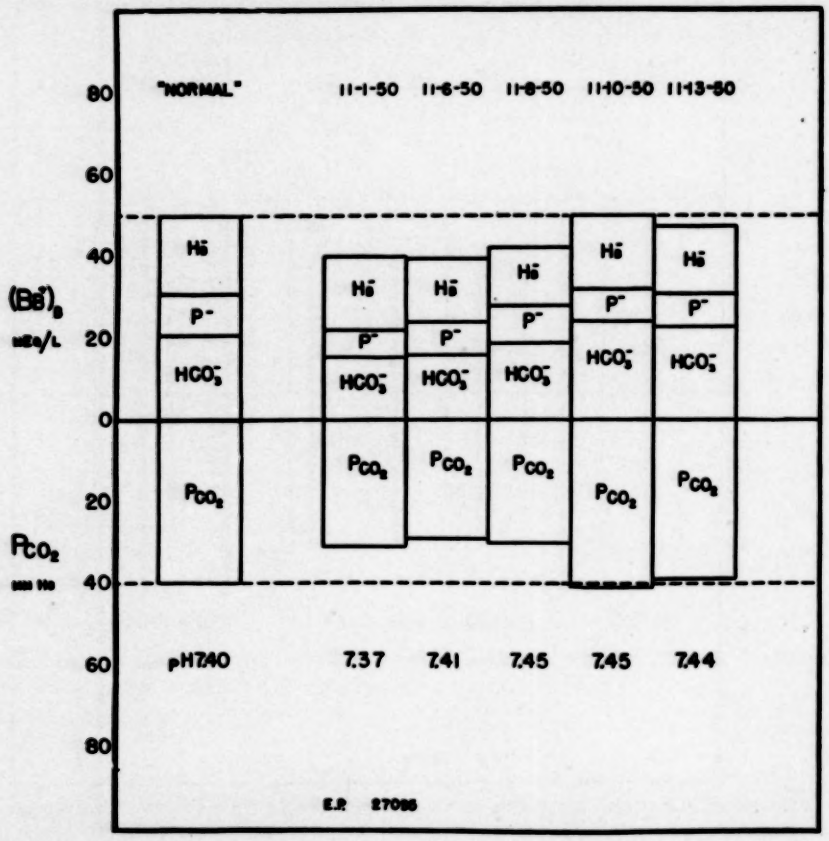

FIG. 4. Acid-base abnormalities in Case III. Hodgkin's disease; oliguria following transfusion reaction.

For the first two hospital weeks the patient passed two to eight liquid stools per day, sometimes blood streaked. On occasion he was nauseated and vomited. He lost weight rapidly. He was given blood transfusions and other parenteral fluids in an attempt to prepare him for further x-ray therapy. On October 25th he received 275 cc. of mismatched blood which resulted in a shaking chill. He became jaundiced the next day and the urine was dark orange in color. For ten days urine output ranged between 600 and 80 cc. The specific gravity fell to 1.015. Diarrhea continued together with vomiting. For the nine-day period preceding death the total output of urine was less than 250 cc. The patient died November 14th, nineteen days after the transfusion reaction. Postmortem examination revealed extensive amyloid infiltration of lymph nodes, kidneys, spleen and liver, lower nephron nephrosis and Hodgkin's disease.

The data on acid-base balance are given in Figure 4 and Tables III and VIII. At the beginning of these observations, November 1st, a deficiency in blood buffer base of 10 mEq./L. existed. There was a diminution in the protein and bicarbonate components of buffer base. Blood pH was not greatly lowered, however, due to decrease in P_{CO_2}; the primary disturbance was metabolic with secondary respiratory changes. Attempts to correct the acid-base disturbance by administration of blood, salt-poor albumin and sodium lactate were successful in restoring the buffer base to normal levels. The blood pH was changed from 7.37 to 7.45. The electrolyte pattern in this patient's serum showed a reduction of total base, $(B^+)_s$, largely due to diminution in the $(Na^+)_s$. The decrease in serum sodium concentration was accompanied with increase in urine sodium. In spite of rising fraction of the undetermined acids, $(X^-)_s$, total fixed

acids, $(A^-)_a$, were not elevated due to regression of $(Cl^-)_a$ as $(HCO_3^-)_a$ was increased under therapy with lactate. The electrolyte pattern was one of fixed base deficit rather than fixed acid excess.

In summary, acid-base abnormalities showed an initial "mixed disturbance" and primary "metabolic acidosis" with secondary "respiratory alkalosis" which disappeared with therapy.

CASE IV. A seventy-one year old retired master sergeant (Hospital No. 26,195) was first admitted to this hospital in 1946 when a diagnosis of chronic pyelonephritis with hypochromic anemia was made. At that time blood non-protein nitrogen was 90 mg. per cent; PSP test showed less than 5 per cent excretion of dye in a two-hour period. Gastrointestinal x-ray revealed no abnormalities. Subsequent admissions confirmed the original diagnosis of severe renal disease with no hypertension. He was admitted on March 6, 1950, because of continuing anemia, requiring transfusions during the previous twelve months, increasing weakness and weight loss, and a two-week history of nausea, vomiting, tarry stools and bleeding from the mouth and nose. Admission physical examination revealed cachexia, dehydration, pallor, evidence of bleeding from oral and nasal mucous membranes, a blood pressure of 180/70 and melena. Respiratory rate was not increased. The fundi and peripheral vessels showed evidence of severe sclerosis. The hemoglobin was 4.8 gm. per cent and the red blood count 1,720,000; the specific gravity of the urine was 1.010 with a trace of albumin and 4 to 6 red cells and 1 to 3 white cells per high power field. The patient was given a soft diet and oral fluids as tolerated. On March 8th he received a transfusion of 500 cc. of citrated blood. Subsequent parenteral fluid therapy during the course of these studies is listed in Table IX. Evidence of bleeding from the gastrointestinal tract subsided during the first two weeks of hospitalization. Intermittent vomiting continued until April 1st. Gastrointestinal x-ray showed presence of a duodenal ulcer with crater, the presumed source of bleeding. At no time was there evidence of pulmonary insufficiency or congestive heart failure. He was discharged April 23rd with the diagnosis of chronic pyelonephritis with uremia, duodenal ulcer with hemorrhage. He returned July 3rd for follow-up examination and treatment. In general he had been well except for occasional vomiting. He felt short of breath on mild exertion. On examination he displayed marked pallor of the skin and mucous membranes but showed no evidences of bleeding. The remainder of the physical examination was the same as on the previous admission. The initial hemoglobin was 3.3 gm. per cent, the red cell count 1,820,000; the blood non-protein nitrogen was 115 mg. per cent. The patient received a blood transfusion of 500 ml. of citrated blood on July 6th, 7th and 8th. The patient was discharged July 16th clinically much improved.

He remained in fair health until November, 1950, when because of weakness he received two transfusions totaling 1,000 ml. of blood. On November 29th bronchopneumonia developed and the patient was hospitalized elsewhere. He was treated with antibiotics with some improvement but suffered a period of unconsciousness with subsequent left-side paralysis. He was transferred to this hospital on December 23rd. On admission the patient was mentally confused. He appeared cachectic and moribund. The oral temperature was 101°F., pulse 112, respirations 24, blood pressure 180/76. The heart was enlarged to percussion, the rhythm irregular. There was pitting edema over the lower back and sacrum. Left facial weakness with slight paralysis of left arm and leg was present. The hemoglobin was 9.9 gm. per cent with a red cell count of 2,470,000. The blood non-protein nitrogen was 112 mg. per cent.

Although the patient's condition had deteriorated markedly since the previous admission, he responded noticeably to parenteral fluid therapy. However, on January 5, 1951, he experienced the first of a series of convulsions which recurred daily and he died on January 9th. Autopsy revealed encephalomalacia due to thromboses, bronchopneumonia and contracted, scarred kidneys with evidence of long-standing pyelonephritis.

The studies on acid-base balance are summarized in Figure 5 and Tables III and IX. A deficit in whole blood buffer base of 10 to 15 mEq./L. persisted throughout the first admission. The primary disturbance was "metabolic" with secondary changes in P_{CO_2}. The buffer base deficit was in the hemoglobin and bicarbonate buffer systems. Attempts to correct this deficit were not successful due to insufficient replacement of hemoglobin and bicarbonate. The use of 1/6 molar lactate solution substantially diminished the deficit of bicarbonate. (Fig. 5, dates 4/7 and 4/10.)

On the second admission, July 10th, the whole blood buffer base was found to be diminished with a considerable diminution in bicarbonate. Although the administration of 2,500 ml. of blood was accompanied with an increase in hemoglobin and protein over values return toward normal of buffer base and P_{CO_2} with lactate therapy.

Case v. A sixty-one year old male (Hospital No. 28,311) was admitted to this hospital for the third time on February 6, 1951, because of increasing shortness of breath and swelling of

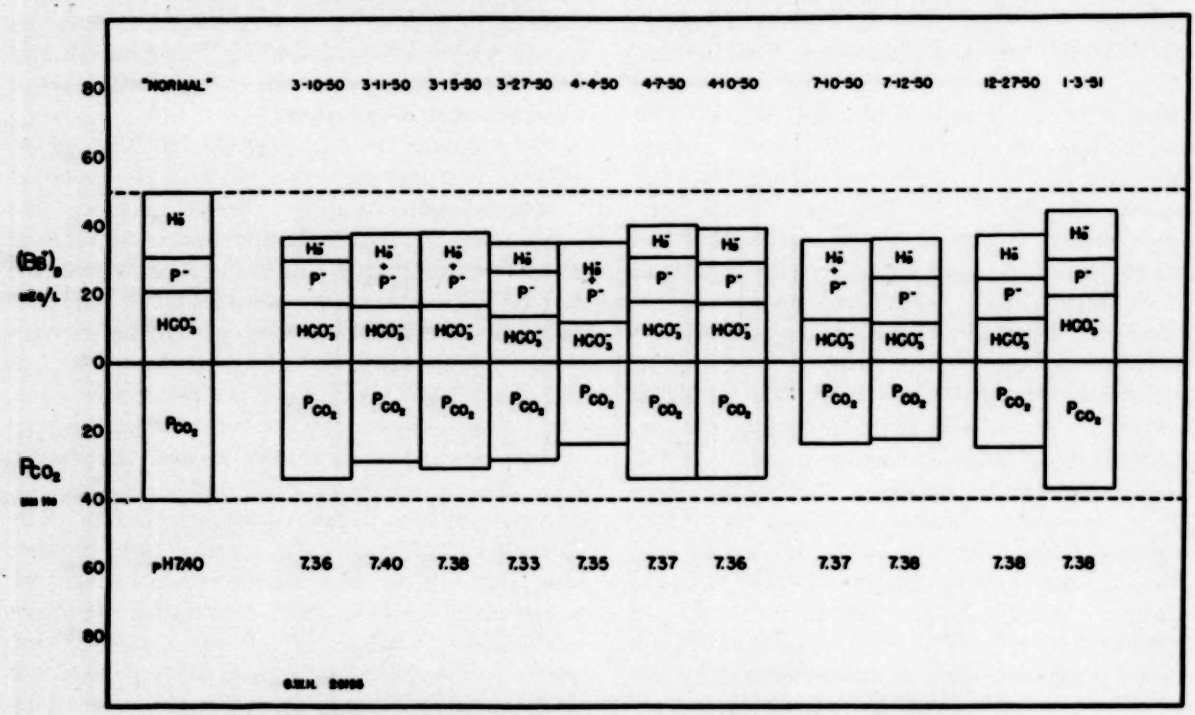

Fig. 5. Acid-base abnormalities in Case iv. Chronic pyelonephritis; uremia.

found at the end of the first admission, there was still a deficiency of 14 mEq. of buffer base, largely attributable to a reduction in bicarbonate.

Acid-base studies on the final admission, December 27th, again revealed diminution in whole blood buffer base confined to the hemoglobin and bicarbonate systems. The administration of blood and 1/6 molar lactate solution was accompanied with an increase in bicarbonate and hemoglobin, without demonstrable changes in pH. The serum electrolyte pattern throughout these studies indicated on most occasions a total base deficit, $(B^+)_e$, with an excess of fixed acids, $(A^-)_e$. (Table ix.) Undetermined acids, $(X^-)_e$, were increased. Under therapy the regression of chloride, $(Cl^-)_e$, with an increase in bicarbonate, $(HCO_3^-)_e$, as found in the previous cases, is again evident.

In summary, acid-base studies revealed a "mixed disturbance," primary "metabolic acidosis" with secondary "respiratory alkalosis," at times an abnormally low blood pH and a the lower legs and feet of two weeks' duration. On previous admissions the diagnosis of arteriosclerotic heart disease with congestive heart failure, pulmonary fibrosis and emphysema had been made. For some months before the present admission the patient had not taken digitalis but had been on a diet restricted in salt; however, his activity had been severely handicapped because of extreme shortness of breath. A chronic cough present for over twenty years, productive of mucopurulent sputum, had persisted.

On admission the temperature was normal, the respiratory rate 40/minute, heart rate 92, blood pressure 160/100. The patient appeared dyspneic and orthopneic; respirations were shallow. Cyanosis of the lips and nail beds was present. The neck veins were distended. Other pertinent physical findings included a rib cage greatly increased in the anteroposterior diameter with almost no respiratory motion. Faint expiratory wheezing was heard over both lung

fields with coarse rales at the lung bases. The heart size was impossible to ascertain by percussion; the liver was palpable 6 cm. below the right costal margin; pitting edema of the lower extremities extended to the buttocks.

During the first week of hospitalization the patient was treated with aminophyllin, mercuhydrin, digitalis and a low sodium diet. Dependent edema disappeared in four days' time.

On the morning of February 7th arterial puncture was done. (Fig. 6, Tables IV and X). The patient was then placed in an oxygen tent and remained in the tent, except for meals, until February 12th. During this period it was noted that he became increasingly confused, particularly at night. Between February 12th and 20th he was allowed out of the tent four hours during each day but was returned to the tent at night. By the 21st his respiratory symptoms had improved to the point where he no longer required oxygen during the day, but he was more comfortable sleeping in the tent.

Acid-base studies in this patient with severe respiratory disease and concomitant subsiding congestive heart failure revealed an increase in the blood buffer base due almost entirely to increase in bicarbonate. There was also a significant increase in arterial P_{CO_2}. CO_2 retention, we believe, was the primary disturbance in the acid-base balance and resulted, presumably, from diminished alveolar ventilation and consequent retention of CO_2. Although oxygen therapy appeared indicated due to the clinical state (primarily severe arterial oxygen unsaturation), it was apparent that this therapy resulted in further increase in P_{CO_2}, with clinical symptoms and signs of mental confusion. With an increase in P_{CO_2} there was increase of bicarbonate which prevented significant shifts in blood pH.

Final studies, February 26th, were done a few minutes after the patient was removed from a night's rest in the oxygen tent. Arterial oxygen unsaturation and increased respiratory rate were accompanied with a lowering of P_{CO_2} without concomitant reduction in bicarbonate. Blood pH therefore was elevated. The serum electrolyte partitions in these studies showed a mild deficit in total base, $(B^+)_e$. However, fixed acids, $(A^-)_e$, were much reduced due to the increase in $(HCO_3^-)_e$ with regression of $(Cl^-)_e$.

Acid-base abnormalities in this case showed an initial "mixed disturbance" and primary "respiratory acidosis" with secondary "metabolic alkalosis" which increased under oxygen therapy without significant change in pH from normal.

CASE VI. A fifty-three year old white male (Hospital No. 27,353) was admitted to this hospital June 29, 1950, because of difficulty in

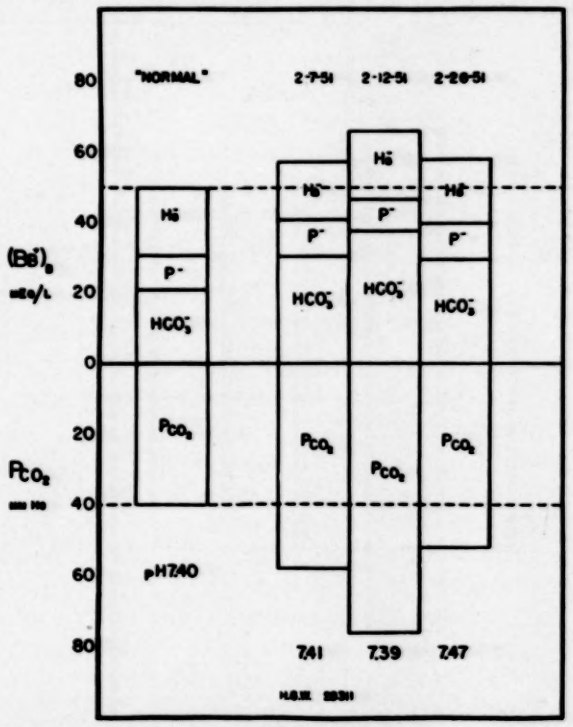

FIG. 6. Acid-base abnormalities in Case V. Pulmonary fibrosis and emphysema; chronic asthmatic bronchitis; arteriosclerotic heart disease and cor pulmonale.

breathing. For many years he had had seasonal attacks of asthma which during the past twelve months had required hospitalization and treatment. On admission the patient appeared cyanotic and mentally confused. The breathing was labored, the respiratory rate 25/minute; the temperature was normal, the heart rate 102, blood pressure 130/70. Advanced pulmonary emphysema was present, with limited respiratory movement of the rib cage. Inspiratory and expiratory wheezes were heard over both lung fields. There was no edema. The hemoglobin was 10.8 gm. per cent. The white cell count was 7,250 with no eosinophils seen. Serum nonprotein nitrogen, chloride, calcium, phosphorus, total protein and A/G ratio were within normal limits. The urine was not remarkable. The patient was placed in an oxygen tent and given intravenous aminophyllin and adrenalin subcutaneously. During the first five hospital days removal from the tent resulted in immediate

development of dyspnea and increased difficulty in breathing. After thirty-six hours of continuous oxygen therapy the patient became extremely drowsy and incontinent of urine. The question of CO_2 narcosis led to studies in acid-base balance on July 3rd. With decreasing oxygen found; however, the pH was in the normal range. The arterial P_{CO_2} was greatly increased. These findings were due to the administration of oxygen during preceding days with reduction of respiratory rate and ventilatory exchange. The primary disturbance was respiratory, which

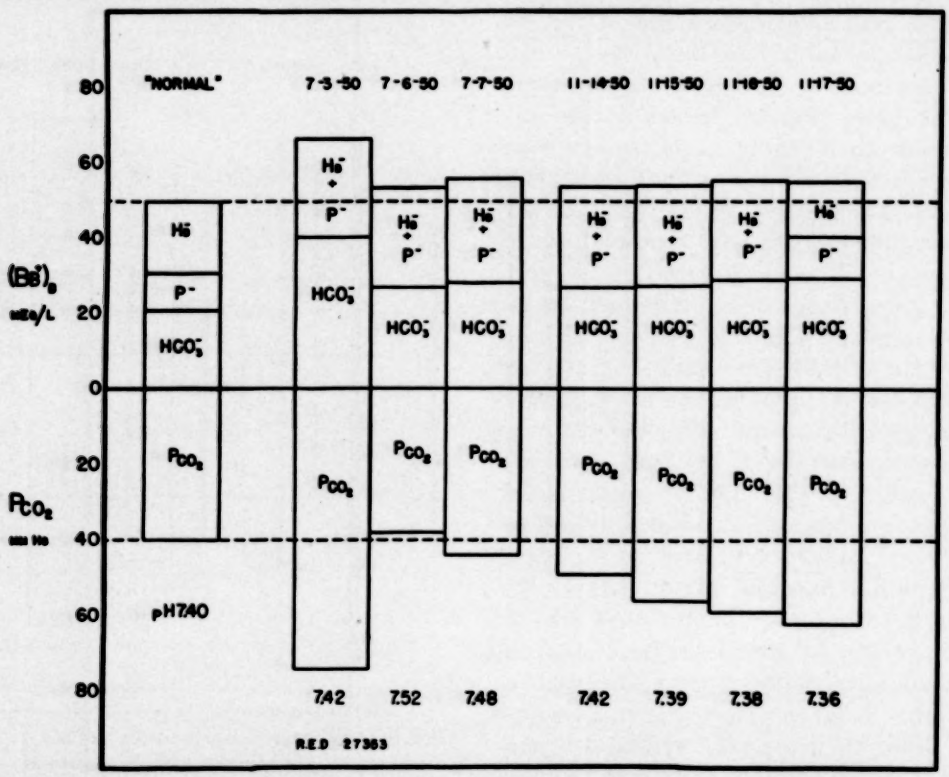

FIG. 7. Acid-base abnormalities in Case VI. Pulmonary fibrosis and emphysema; asthmatic bronchitis.

therapy gradual improvement occurred in the next four days. The vital capacity on July 6th was 1,750 cc. At the time of discharge on the 19th it had increased to 2,650 cc.

On November 3rd the patient was readmitted because of a recurrence of severe asthma. Physical examination was essentially unchanged from that of the previous admission except that he was not confused. He responded slowly to intravenous aminophyllin, nasal oxygen, ephedrine and sedation. It was decided to study the effect of continuous oxygen administration on the acid-base balance of the blood. On November 14th, before oxygen therapy was begun, base-line studies were carried out. During the next three days the patient remained in the oxygen tent except for meals.

Studies on acid-base balance are presented in Figure 7 and Tables IV and XI. On July 3rd increased CO_2 content of the whole blood was resulted in a secondary increase in blood buffer base consisting of an increase in bicarbonate. On July 6th, under conditions of increased respiratory rate and arterial oxygen unsaturation, the CO_2 content of the blood was lower; the pH showed a state of alkalosis. Arterial P_{CO_2} was greatly decreased over that of the previous observation. On July 7th, breathing 50 per cent oxygen, the arterial oxygen saturation had risen to 95 per cent; the P_{CO_2} was increasing and the pH was therefore lower.

The studies during the second admission, November 14th to 17th, show the changes in buffer base, pH, and P_{CO_2} effected by almost continuous oxygen therapy. The primary disturbance, the increase in P_{CO_2}, involved secondary changes in bicarbonate which, however, lagged slightly behind the more rapid changes in P_{CO_2}. Consequently, during the period of adjustment a fall in pH occurred.

TABLE V

DISTRIBUTION OF ELECTROLYTES BETWEEN CELLS AND SERUM*

	Date	Vc	pH	Hb(mM)	% O_2 Sat.	$B^+(HbO_2^-)_b$ mEq./L.	$B^+(Hb^-)_b$ mEq./L.	$B^+(Hb_t^-)_b$ mEq./L.	$B^+(Hb_t^-)_c$ mEq./L.	$B^+(Pr^-)_c$ mEq./L.	$(CO_2)_b$ mM/L.	$(H \cdot HCO_3)_c$ mM/L.	$(HCO_3^-)_b$ mEq./L.	$(HCO_3^-)_c$ mEq./L.	$(Cl^-)_b$ mEq./L.	$(Cl^-)_s$ mEq./L.	$(Cl^-)_c$ mEq./L.	$(X^-)_s$ mEq./L.	$(B^+)_s$ mEq./L.	$(B^+)_s$ mEq./L.
"Normal"	.....	.45	7.40	9.0	98	18.1	0.3	18.4	40.9	17.0	21.9	1.30	20.7	25.1	16.4	83.0	104.0	83.5	5.0	162.0	111.3
Case No.																					
I	11/29/50	.33	7.32	6.3	97	11.4	0.3	11.7	35.4	15.3	10.1	0.66	9.5	10.8	7.5	86.8	98.9	62.1	13.2	138.2	118.3
	12/4	.34	7.50	6.8	89	14.0	1.3	15.3	45.0	12.7	22.3	1.00	21.4	25.0	15.0	71.6	84.6	46.4	21.5	143.9	127.9
	12/8	.39	7.52	7.3	88	15.0	1.7	16.7	42.8	12.9	22.7	1.01	21.7	26.0	16.0	61.8	76.5	38.8	18.0	133.4	115.6
IV	3/10/50	.13	7.36	2.6	60	3.2	1.5	4.7	36.2	11.7	18.2	1.05	17.2	18.5	9.3		99.4	40.8	16.6	146.2	102.9
	4/7	.20	7.37	4.7	101	9.4	...	9.4	32.4	13.5	18.6	1.05	17.6	19.5	14.0	83.6	94.0	58.1	13.8	140.8	118.3
V	2/7/51	.43	7.41	7.9	73	12.1	3.4	15.5	36.0	16.3	31.7	1.80	30.0	36.3	23.3	60.2	88.9	43.1	1.9	143.4	104.3
	2/12	.50	7.39	8.9	92	16.7	1.1	17.8	35.6	16.2	39.1	2.37	36.9	45.3	30.5	62.0	78.5	45.5	7.6	147.6	119.2
	2/26	.45	7.47	8.3	76	14.0	3.6	17.6	39.1	16.2	30.8	1.62	29.3	36.3	22.1	60.6	89.6	45.2	4.9	147.0	111.3

* The data on this table from which Figures 8, 9 and 10 are constructed were derived from the whole blood and serum analyses given in Tables VI through XI in the Appendix. The methods for calculation of these data are given in the Appendix. For definition of symbols see Table I.

On the day of the final studies the serum electrolyte pattern was normal with respect to total base, $(B^+)_s$; however, there was a deficit in fixed acids, $(A^-)_s$, due to increase in $(HCO_3^-)_s$. The electrolyte pattern was one of fixed acid deficit without base excess.

In summary, initial acid-base balance studies showed a "mixed disturbance," primary "respiratory acidosis" with secondary "metabolic alkalosis" and a normal pH. These changes produced by oxygen therapy regressed to a condition of "metabolic alkalosis" upon withdrawal of oxygen. Subsequent observations revealed an increasing primary "respiratory acidosis" with a fall in pH due to oxygen therapy.

PART III

Distribution of Ions between the Serum and the Red Blood Cells. The data on three patients (Table v) have been charted after the manner of Hastings[11] in Figures 8, 9 and 10. Although calculations of certain ionic constituents of the red cells have been derived from analyses of whole blood and serum, information concerning serum water and cell water was not available. Also, the total base concentration of the red cells was not determined directly. In the absence of measurements of phosphate and undetermined anions in the red cell these components have been assumed to be of equal concentration in red cells and serum. Total red cell base has been calculated as the sum of the calculated and undetermined anions. (For calculations see Appendix.)

In Case I (Fig. 8) the studies reveal the electrolyte changes typical of uremic acidosis with a diminished concentration of serum bicarbonate, serum chloride and serum total base. There was a diminished base-binding capacity of hemoglobin but an apparent increase in the total base concentration of the red blood cells. The simultaneous changes in the concentrations of serum and red blood cell chloride are apparent. The administration of lactate and whole blood effected the increase in the bicarbonate concentration of cells and serum, an increase in the base-binding capacity of hemoglobin and an increase in the blood pH. The changes in the readily diffusible anions, chloride and bicarbonate, are consistent with the predictions of the Donnan equilibrium.[12,13]

Case IV (Fig. 9) represents the changes in the blood serum and cells on March 10 and April 7,

1950. The marked diminution in the volume of red blood cells in both observations is apparent. On March 10th the serum reveals a diminished concentration of total base, chloride, bicarbonate and a diminished base-binding capacity of the proteins. The undetermined anion concentration is increased as it was in Case I. The red blood cells reveal a diminution in the concentration of total base, chloride, bicarbonate and base-binding capacity of the hemoglobin but an increased concentration in the undetermined anions. These findings are similar to those in Case I but are of greater degree. On April 7th the volume of red cells is increased and the volume of plasma is diminished due to transfusions. The serum concentrations of bicarbonate and chloride remain at a subnormal level. The base-binding capacity of the protein is very slightly increased. The undetermined anion concentration is diminished. The total base of

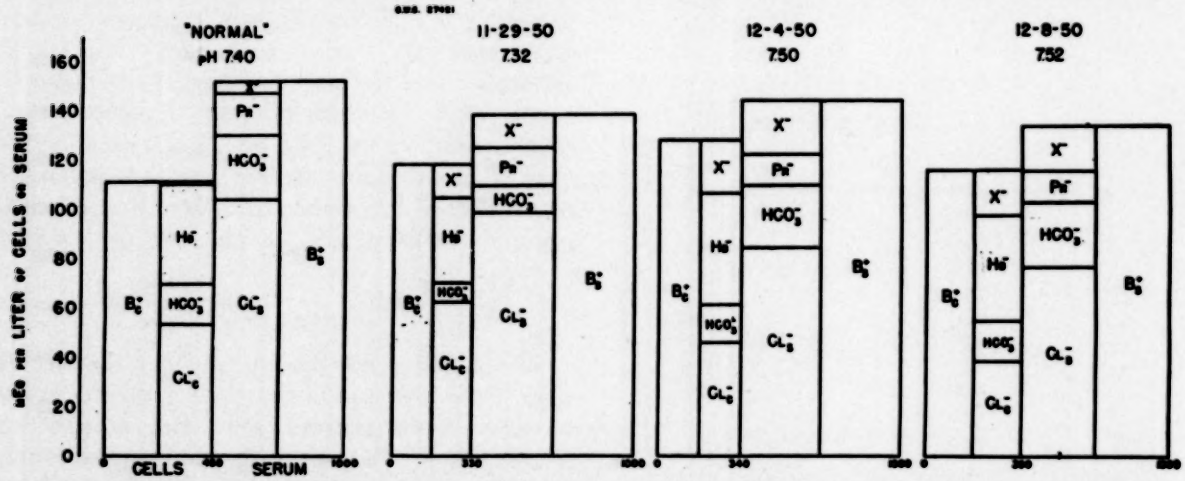

FIG. 8. Distribution of ions between red blood cells and serum in Case I. (Constructed after the manner of Hastings.[11]) Hypertensive cardiovascular renal disease. The data for this figure and Figures 9 and 10 are given in Table V. For explanation of symbols see Table I and Appendix. On the abscissa is plotted 1 L. of blood divided into the volume of cells and serum as given by the hematocrit. On the ordinate is plotted the concentration in mEq./L. of the component parts of red blood cells or serum. Blood pH and the dates are given at the top. On the left the "normal" based on the work of Dill et al.[9] is given.

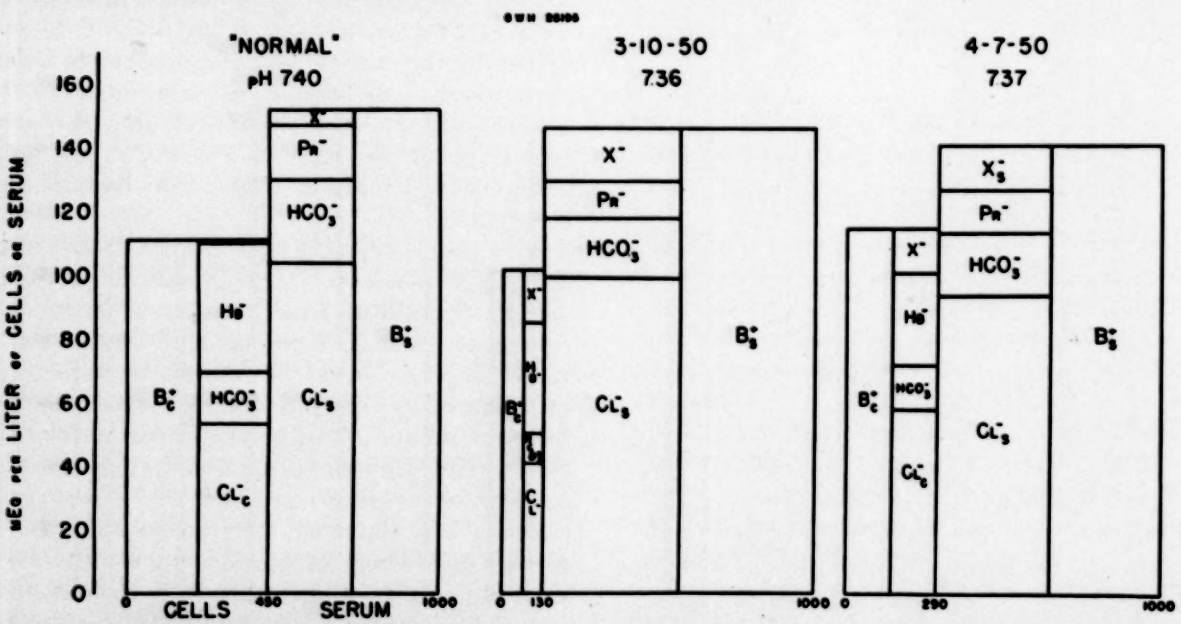

FIG. 9. Distribution of ions between red blood cells and serum in Case IV. Chronic pyelonephritis; uremia. For explanation see Figure 8 and text.

the serum is likewise decreased. The concentration of the total base of the red blood cells has increased, accompanied with an increased concentration of chloride and bicarbonate but no increase in the base-binding capacity of the red cell hemoglobin. There was slight diminution in the undetermined anion concentration of the red blood cells.

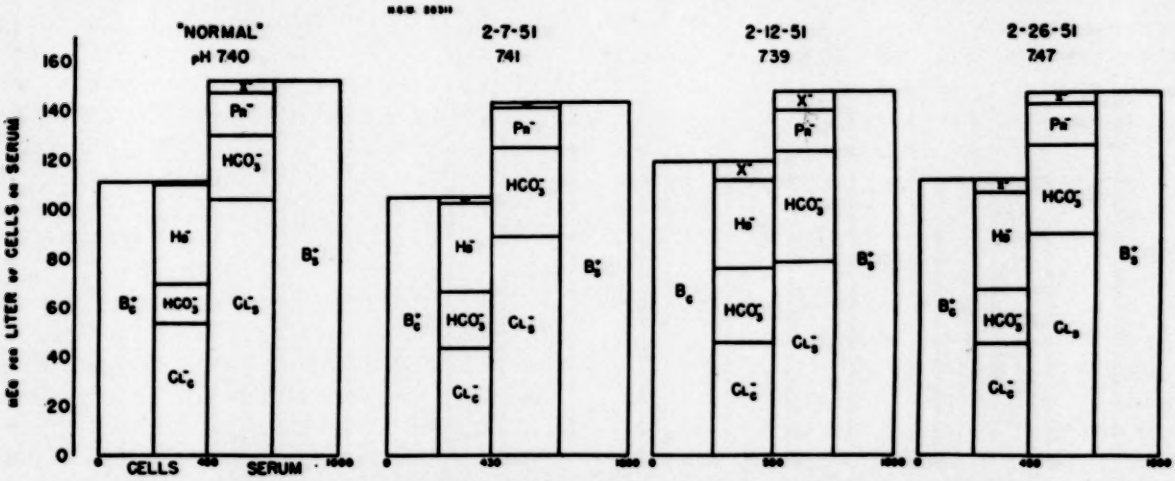

FIG. 10. Distribution of ions between red blood cells and serum in Case v. Pulmonary fibrosis and emphysema; chronic asthmatic bronchitis; cor pulmonale. For explanation see Figure 8 and text.

In summary, initial studies in this patient, March 10th, show the changes due to greatly reduced red cell volume, the diminution in the portion of the whole blood buffer base contributed by hemoglobin in severe anemia and the increase in this fraction effected by transfusions. The width of the rectangle Hb^-, April 4th, indicates this increase.

Case v (Fig. 10) shows the electrolyte pattern in serum and cells in the presence of increased CO_2 pressure and arterial oxygen unsaturation and the changes which follow further increase in CO_2 pressure and increased arterial oxygen saturation induced by oxygen therapy. Before oxygen therapy, February 7th, total base of red cells and serum was diminished. Base bound by hemoglobin was slightly reduced due primarily to arterial oxygen unsaturation. Although total base of the red cells was reduced, buffer base of red cells, hemoglobin and bicarbonate were not reduced because of recession of chloride. Serum buffer base was increased due to increase in bicarbonate and recession of chloride. After five days of oxygen therapy, February 12th, when arterial oxygen saturation was normal but CO_2 pressure had increased greatly, the buffer base of red cells and serum had increased further. The increase in undetermined anions on that date was not satisfactorily explained on the basis of significant deviation in pH and oxygen unsaturation. On February 26th, when arterial oxygen unsaturation was again present and CO_2 pressure was reduced, buffer base of red cells and serum approximated values found on February seventh.

In summary, the derived data on intracellular ionic constituents appeared to indicate an increase in diffusible buffer anion bicarbonate and a corresponding recession of diffusible nonbuffer anion chloride when serum bicarbonate was increased by intravenous lactate therapy. A rise in pH increased the base bound by hemoglobin per liter of cells. Transfusion therapy increased the base bound by hemoglobin per liter of whole blood. Increase in serum bicarbonate associated with increased CO_2 pressure also appeared to increase red cell buffer base by increase in bicarbonate. The increase in total red cell base in these cases may be more apparent than real for reasons stated previously.

REMARKS

The inherent dangers in drawing inferences from a determination of the plasma CO_2 content or CO_2 combining power as to the presence of acidosis and alkalosis were emphasized by Van Slyke and Cullen,[14] Peters and Van Slyke,[1] and Clark.[15] Singer and Hastings[3] state, "Furthermore the almost universal practice of limiting the laboratory determination to a plasma CO_2 content or CO_2 combining power

has these serious drawbacks: (1) A mistake in diagnosis is possible. (2) The magnitude of the disturbance and the state of other essential factors in the acid-base balance can only be approximated. (3) Because the magnitude of the disturbance cannot be estimated precisely, it is difficult to evaluate the effects of different forms of treatment." Also, as these authors were careful to point out, the plasma CO_2 content alone gives no information concerning the concentration of other important buffer systems.

The information obtained from the studies set forth in this paper has confirmed the known fallacy of predicting the state of the acid-base balance of the blood when only the CO_2 content of whole blood is known.

The data from Cases I to IV show that pH was within normal limits when the whole blood buffer base exceeded 40 mEq./L. Buffer base values between 36 and 39 mEq./L. were associated with pH values in the normal or low-normal range. Acidosis was present, however, when the whole blood buffer base was 33 to 35 mEq./L. These observations on the concentration of buffer base and the development of acidosis agree in general with those of Singer.[4]

It is of interest to note that a depletion of buffer base of 10 to 17 mEq./L. calls forth the anticipated lowering of P_{CO_2} but that in three instances this respiratory adjustment to primary metabolic disturbances was not sufficient to maintain pH within the normal range. However, the reduction in P_{CO_2} was not maximal nor even accompanied with changes in respiratory function which could be recognized clinically. Therefore, one may surmise that a pH in the range of 7.33 does not call forth a maximum respiratory response for the regulation of P_{CO_2} in some patients who suffer from long-standing deficiency in buffer base.

Buffer base deficits in these four patients were due chiefly to reduction in hemoglobin and bicarbonate buffer systems although in Case III there was a severe deficit in protein. Attempts at restoration of blood buffer base by replacement of deficient components through transfusions, administration of bicarbonate by mouth or ⅙ molar lactate solution intravenously were successful in three of the four patients. The patient in Case IV received no bicarbonate until after April 5th but received numerous transfusions. From the data in this case it is evident that mild or incipient acidosis with reduction in buffer base persisted throughout much of the period of study. In retrospect, it appears likely that acidosis could have been corrected by the administration of more ⅙ molar lactate.

Case II was of particular interest because of the clinical improvement following therapy. The striking regression of symptoms could not be correlated with bed rest, rise in hemoglobin, lowering of non-protein nitrogen or fixed acids, or change in pH. The impression was strong, however, that the return of buffer base and P_{CO_2} toward normal was responsible for a most gratifying remission of distressing symptoms.*

From these studies of primary metabolic disturbances it was clear that a rapid restoration of whole blood buffer base to normal values was achieved by the use of sodium lactate intravenously. However, it was evident that the bicarbonate increase was of short duration. For this reason and because hemoglobin, at physiologic pH, provides buffer base commensurate with that of bicarbonate, attempts to restore significant deficit in hemoglobin should be made. Hemoglobin has the added advantage over bicarbonate of being an effective buffer of carbonic acid as well as fixed acids.

With regard to lactate therapy, the development of alkalosis in Case II is of interest. The data from this case on December 4th and 8th show a normal arterial CO_2 content and whole blood buffer base, but a pH above the normal range. Arterial CO_2 pressure was reduced. Likewise, arterial oxygen unsaturation was present. In the light of the clinical course the following hypothesis for the development of alkalosis seems reasonable: On December 4th and 8th considerably more pulmonary congestion was present than was suspected clinically. This brought about alteration in pulmonary dynamics, most likely perfusion without ventilation, the result of which was a mild degree of arterial unsaturation and increased ventilatory rate. Arterial CO_2 pressure, although increased over the previous determination on November 29th, was prevented by the respiratory effect of pulmonary congestion and anoxemia from increasing sufficiently to counter the increase in

* This patient underwent operation for relief of intrarenal tension of the left kidney in May, 1951; numerous large cysts were found in the renal parenchyma which were evacuated. Before and following operation complete blood acid-base balance studies were performed. In the absence of acidosis restoration of whole blood buffer base to normal values by transfusion and ⅙ molar lactate therapy had a profoundly salutary effect on clinical symptoms.

bicarbonate. In this situation the continuation of lactate therapy prevented regression of bicarbonate and effectively perpetuated the alkalosis.

The studies on Cases v and vi show that there was no deviation of blood pH from the normal range with values of CO_2 pressure as high as 76 mm. Hg. This was true only when the increase in P_{CO_2} was gradual and only insofar as a secondary increase in $(HCO_3^-)_e$ accompanied the increase in P_{CO_2}. The rapid development of acidosis in patients undergoing therapy with high concentrations of oxygen has been explained on the basis that increase in $(HCO_3^-)_e$ brought about either by renal excretion of $(Cl^-)_e$ or retention of fixed base, $(B^+)_e$, takes longer than do changes in P_{CO_2}. Until such adjustments are made, increase in P_{CO_2} results in acidosis. The data on Case v, February 7th and 12th, support this concept. It appears impossible to define a range of CO_2 pressure beyond which acidosis will develop since deviation in pH_e depends upon two variables, P_{CO_2} and $(HCO_3^-)_e$.

The effect on pH of a rapid reduction of P_{CO_2} is illustrated by the data from Case v, February 26th, and Case vi, July 6th, in the presence of arterial oxygen unsaturation. P_{CO_2} was reduced from levels present while breathing oxygen but reduction in $(HCO_3^-)_e$ had not taken place so rapidly. Consequently, pH was elevated. The data on Case vi from November 15th to the 17th illustrate the effects of increasing CO_2 pressure on pH when $(HCO_3^-)_e$ was comparatively unaltered.

Earlier, reference was made to the important relations between whole blood buffer base, P_{CO_2}, and the cation-anion pattern of the serum. While graphic presentation of the buffer base, pH and P_{CO_2} is available from the nomogram devised by Singer and Hastings,[3] and Singer[4] as well as from the figures presented in this study, if one is to distinguish between fixed acid excess and base deficit or fixed acid deficit and base excess, data on the total cation-anion pattern of the blood are required. This information is important when treating patients with diabetes, renal disease, vomiting, diarrhea or fistulas from the gastrointestinal tract in whom the primary disturbance is in the metabolic component of acid-base equilibria and in whom electrolyte replacement therapy is so often necessary. In Cases i and iii there was an increase in the undetermined acids, $(X^-)_e$, of the serum usually found in patients with advanced renal disease. There was also a reduction in total base in both patients. In spite of increasing concentration of $(X^-)_e$ throughout the period of the observations there was no abnormal increase in total fixed acids because recession of $(Cl^-)_e$ accompanied increasing $(X^-)_e$. Diminution in buffer base in these patients was due to diminution in total base, B^+, and not to excessive retention of fixed acids. The electrolyte pattern in these cases defined the metabolic disturbance initially as one of fixed base deficit. Later studies in these two patients showed that although the concentration of total base remained low, increase in $(HCO_3^-)_e$ with corresponding recession of $(Cl^-)_e$ was the predominant mechanism in restoration of the whole blood buffer base to normal values. In terms of serum electrolyte concentration, however, the final picture was one of fixed base *and* fixed acid deficit.

The electrolyte data from Cases ii and iv indicate that the prevailing cation-anion disturbance was one of fixed acid excess with at times a small base deficit.

The relation between whole blood buffer base, P_{CO_2}, and serum electrolyte patterns in respiratory disturbances is illustrated by the data from Case v. In this patient buffer base was increased, especially following oxygen therapy, and the increment was largely in $(HCO_3^-)_e$. $(Cl^-)_e$ was correspondingly reduced. Total base, $(B^+)_e$, was not increased. The primary disturbance affecting acid-base equilibria in this patient was CO_2 retention which would have resulted in acidosis had there not been a reduction in $(Cl^-)_e$ and an increase in bicarbonate, $(HCO_3^-)_e$. The electrolyte pattern was one of fixed acid deficit. These changes illustrate the secondary deviations in metabolic components of acid-base equilibria which are under renal control.

SUMMARY

Intensive studies on acid-base balance of the blood have been made on four patients with renal disease and two patients with respiratory disease. Applying the concepts of Singer and Hastings, the data have been interpreted in terms of the two physiologically important variables, namely, the whole blood buffer base and CO_2 tension. The clinical value of this simplified method of interpretation has been demonstrated. The whole blood buffer base is

the metabolic component and the CO_2 tension the respiratory component of the acid-base balance of the blood. In these studies a primary increase or decrease in one variable was followed with a secondary increase or decrease in the other. When the secondary response was not sufficient to re-establish normal equilibrium between the two variables, a shift in pH occurred.

In evaluating and correcting clinical acid-base abnormalities these studies emphasize the need for consideration of all the components of the blood buffer base, i.e., hemoglobin, serum proteins and phosphate as well as bicarbonate.

The data on the ionic constituents of the red cells showed an increase in the diffusible buffer anion bicarbonate and recession of diffusible non-buffer anion chloride in patients treated with ⅙ molar lactate. Under increased CO_2 tension the increase in serum bicarbonate was associated with increase in red cell bicarbonate. Transfusions increased the base bound by hemoglobin per liter of whole blood. A rise in pH increased the base bound by hemoglobin per liter of cells.

The studies portray the relation between the blood buffer base, CO_2 tension and serum cation-anion pattern. The patients with renal disease revealed deficiencies in the bicarbonate component of the blood buffer base resulting from fixed base deficit or fixed acid excess or both. Treatment of these patients by intravenous ⅙ molar lactate solution or oral sodium bicarbonate was followed with return of bicarbonate values toward normal and decrease of fixed acid excess due to regression of chloride. The two patients with respiratory disease accompanied with arterial oxygen unsaturation and elevated CO_2 tension showed high blood bicarbonate values and fixed acid deficits. The data from these patients showed increasing CO_2 tension under oxygen therapy with corresponding increase in bicarbonate values and increase in fixed acid deficit.

APPENDIX

Methods and Tables of Raw Data. Blood samples were drawn during the fasting state except on a few occasions when it was necessary to take blood for gas analyses two hours after a meal. For gas analyses arterial blood was drawn anaerobically into 10 cc. Luer-Lok syringes, lightly oiled and previously rinsed with 0.2 cc. of heparin solution (10 mg. sodium heparin per cc.). The syringes were capped with a mercury seal and placed in ice water. Immediate analyses of CO_2 content, O_2 content and O_2 capacity were carried out in duplicate. The blood samples for the determination of pH and serum chloride were also collected anaerobically in lightly oiled syringes.

When difficulties prevented obtaining sufficient arterial blood, venous blood was used. This is noted in Tables VI–XI. On such occasions venous blood was drawn, without stasis, as soon as the arterial puncture was completed. Serum chloride and bicarbonate concentrations were always determined on the same type of blood, arterial or venous.

The following laboratory methods were employed: Blood pH was determined anaerobically at 38°C. by the method of Behrman and Fay,[16] modified; carbon dioxide content, oxygen content and oxygen capacity of the blood, Van Slyke and Neill;[17] hemoglobin was calculated from the oxygen capacity of the blood;[17] the hematocrit, Wintrobe,[18] using the correction for trapped plasma applied by Barnes;[19] non-protein nitrogen of the blood, Koch and McMeekin;[20] serum total protein, albumin and globulin partition, Labby and Hoagland[21] and Hoagland;[22] serum phosphorus, Fiske and Subbarow;[23] serum magnesium, Kunkel, Pearson and Schweigert;[24] serum calcium, Clark and Collip;[25] serum chloride, Van Slyke and Hiller;[26] whole blood chloride, Van Slyke;[27] serum sodium, Butler and Tuthill[28] and the flame photometer; serum potassium, Kramer and Tisdall[29] and the flame photometer.

Calculations. The calculations employed in determining the component parts of the whole blood buffer base, $(B_B^+)_b$*:* The whole blood buffer base, $(B_B^+)_b$, the partial pressure of CO_2, P_{CO_2}, and the serum bicarbonate concentrations, $(HCO_3^-)_s$, were determined from the nomogram of Singer and Hastings.[3] The whole blood bicarbonate, $(HCO_3^-)_b$, was calculated from the total carbon dioxide content of the whole blood, $(CO_2)_b$, and its carbonic acid concentration, $(HHCO_3)_b$. The carbonic acid concentration of the whole blood, $(HHCO_3)_b$, was calculated from the water content of the cells, $(H_2O)_c$, assumed to be 720 gm./L.; the water content of the serum, $(H_2O)_s$, assumed to be 936 gm./L.; and the partial pressure of CO_2, using the data of Dill et al.[30] The base bound by the serum proteins, $(Pr^-)_s$, was calculated from the data of Van Slyke et al.[10] The hematocrit, Vc, and the base bound by the serum proteins per liter of serum were

TABLE VI

CASE I

Date 1950	pH_a	Ve	$(CO_2)_b$* mM/L.	O_2 cap. Vol. %	O_2 cont. Vol. %	O_2 sat. %	Hb gm. %	$(B_B^+)_b$* mEq./L.	P_{CO_2} mm.	$(Na^+)_a$ mEq./L.	$(K^+)_a$ mEq./L.	$(Ca^{++})_a$ mEq./L.	$(Mg^{++})_a$ mEq./L.	$(B^+)_a$ mEq./L.	$(Cl^-)_a$ mEq./L.	$(HCO_3^-)_a$ mEq./L.	$(Pr^-)_a$ mEq./L.	$(X^-)_a$ mEq./L.	$(HPO_4^{--})_a$ mEq./L.	$(Cl^-)_b$ mEq./L.	NPN mg. %	Total Serum Protein gm./L.	Serum Albumin gm./L.	Serum Globulin gm./L.	Remarks
11/29	7.32	.33	10.1	14.0	13.7	97.4	10.5	33.0	21.5	127.0	5.2	4.0	2.0†	138.2	98.9	10.0	15.3	9.7	3.5	86.8	126	62.0	44.5	17.5	Weakness, mental confusion, nausea and vomiting
12/4	7.50	.34	22.3	15.2	13.4	88.6	11.3	49.7	32.0	135.3	3.6	3.0	2.0†	143.9	84.6	25.0	12.7	18.0	3.5	71.6	130	47.8	32.6	15.2	500 ml. blood 11/30, 12/1; 1,000 ml. ⅙ molar lactate 11/30, 12, 1, 12/2, 12/3; 2,000 ml. 5 % dext./H_2O 11/29; 1,000 ml. 11/30; 12/1, 12/2, 12/3; no vomiting; mental confusion less obvious; fluid intake p.o. less than 100 ml./24 hr.; urine output 1,200–2,000 ml./24 hr.
12/8	7.52	.39	22.7	16.4	14.5	88.2	12.2	50.7	33.0	125.0	3.8	2.6	2.0†	133.4	76.5	26.0	12.9	15.7	2.3	61.8	96	48.7	32.8	15.9	500 ml. blood 12/5; 12/6; 500 ml. 1/6 molar lactate 12/5, 12/7; 500 ml. normal saline 12/5, 12/6; 2,000 ml. 5 % dext./H_2O 12/4, 12/5, 2500 ml. 12/6, 12/7; increasing weakness and confusion; no vomiting; fluid intake p.o. less than 100 ml./24 hr.; urine output 1,000–2,000 ml./24 hr.

Clinical diagnosis: Hypertensive cardiovascular renal disease. The blood samples analyzed are arterial except as noted

* Corrected for O_2 saturation below 90 %

† Assumed value

‡ Venous sample

TABLE VII

CASE II

Date 1951	pH_s	Vc	$(CO_2)_b$* mM/L.	O_2 cap. Vol. %	O_2 cont. Vol. %	O_2 sat. %	Hb gm. %	$(B_B^+)_b$* mEq./L.	P_{CO_2} mm.	$(Na^+)_s$ mEq./L.	$(K^+)_s$ mEq./L.	$(Ca^{++})_s$ mEq./L.	$(Mg^{++})_s$ mEq./L.	$(B^+)_s$ mEq./L.	$(Cl^-)_s$ mEq./L.	$(HCO_3^-)_s$ mEq./L.	$(Pr^-)_s$ mEq./L.	$(X^-)_s$ mEq./L.	$(HPO_4^=)_s$ mEq./L.	$(Cl^-)_b$ mEq./L.	NPN mg. %	Total Serum Protein gm./L.	Serum Albumin gm./L.	Serum Globulin gm./L.	Remarks
1/8	7.33	.31	11.9	13.3	13.1	98	9.9	34	24	136.7‡	4.8‡	4.0‡	1.2‡	146.7‡	103.1	12.6	15.3	11.0	4.7‡	87.2	183	62.9‡	42.1‡	20.8‡	500 ml. blood 1/5; morning nausea with occasional vomiting before breakfast and severe leg cramps
1/12	7.42	.29	17.0	12.7	12.1	96	9.5	40	29	138.9‡	4.5‡	3.8‡	1.1‡	148.3‡	100.1	18.0	14.3	11.7	4.2‡	86.6	189	57.3‡	35.4‡	21.9‡	$NaHCO_3$ 2.5 gm. 1/8, 1/9; 10 gm. 1/10; 7.5 gm. 1/11; nausea diminished; no vomiting; leg cramps less severe
1/15	7.41	.34	20.2	15.3	14.6	96	11.4	45	35	140.8	4.5	3.5	1.2	150.0	95.8	22.0	15.2	12.7	4.3	78.4	179	60.1	41.3	18.8	1,000 ml. blood 1/12; $NaHCO_3$ 12.5 gm. 1/12, 16 gm. 1/13, 12 gm. 1/14; 500 ml. blood following arterial puncture 1/15; much improved symptomatically
2/9	7.41	.29	14.0	12.9	12.2	95	9.6	38	24	138.2‡	4.4‡	3.8‡	1.3‡	147.7‡	98.0	15.0	16.8	12.1	5.8	84.2	188‡	67.8‡	43.4‡	24.4‡	Morning nausea, vomiting, severe leg cramps have returned; $NaHCO_3$ 2.5 gm. 2/8
2/21	7.40	.32	19.2	15.0	14.1	94	11.2	44	34	140.1‡	4.4‡	3.5‡	1.1‡	149.1‡	97.8	21.0	15.6	9.2	5.5	80.8	167‡	63.0‡	39.2‡	23.8‡	500 ml. blood 2/9, 2/10, 2/11, 2/19; severe left-sided abdominal pain, 2/9, with gross hematuria, gradually diminishing to 2/21; $NaHCO_3$ 10 gm. daily 2/11–2/21; nausea and leg cramps much improved from 2/12–2/21

Clinical diagnosis: Polycystic kidney disease; uremia. For explanation of superscripts see Table VI.

TABLE VIII

CASE III

Date 1950	pH_s	Vc	$(CO_2)_b$* mM/L.	O_2 cap. Vol. %	O_2 cont. Vol. %	O_2 sat. %	Hb gm. %	$(B_B^+)_b$ mEq./L.	P_{CO_2} mm.	$(Na^+)_s$ mEq./L.	$(K^+)_s$ mEq./L.	$(Ca^{++})_s$ mEq./L.	$(Mg^{++})_s$ mEq./L.	$(B^+)_s$ mEq./L.	$(Cl^-)_s$ mEq./L.	$(HCO_3^-)_s$ mEq./L.	$(Pr^-)_s$ mEq./L.	$(X^-)_s$ mEq./L.	$(HPO_4^-)_s$ mEq./L.	$(Cl^-)_b$ mEq./L.	NPN mg. %	Total Serum Protein gm./L.	Serum Albumin gm./L.	Serum Globulin gm./L.	Remarks
11/1	7.37‡	.35‡	15.9	13.5	13.4	99	10.1	40.0	31	125.0‡	2.6‡	4.0‡	2.0†‡	133.6‡	89.0‡	17.4‡	6.7‡	16.6‡	3.9‡	75.4‡	72‡	29.9‡	11.9‡	18.0‡	500 ml. blood 10/30; 2,000 ml. 10 % dext./sal., 2,300 ml. 10 % dext./H_2O, 1,000 ml. vomitus, 2,000 ml. stool, 10/29–10/31; 1,460 ml. oral fluid 10/29–10/31
11/6‡	7.41	.32	16.6	14.2	7.6	53	10.6	39.4	29	126.3	3.1	3.3	2.0†	134.7	89.5	18.0	7.3	15.4	4.5	72.6	113	32.1	12.4	19.7	500 ml. blood 11/3; 1,200 ml. 10 % dext./sal., 3,500 ml. 10 % dext. H_2O, 360 ml. vomitus, 1,000 ml. stool 11/1–11/5; no oral fluid 11/3–11/5
11/8‡	7.45	.27	19.7	11.0	7.2	65	8.2	42.3	30	129.2	2.8	3.7	2.0†	137.7	88.6	21.0	9.5	15.7	2.9	77.8	130	37.0	24.5	12.5	500 ml. blood 11/6, 100 gm. human serum albumin 11/6–11/7, 500 ml. ⅙ molar lactate 11/7; 240 ml. vomitus, 100 ml. stool 11/6–11/7; no oral fluid
11/10‡	7.45	.33	25.5	13.6	6.8	50	10.1	50.0	41	134.8	2.6	3.8	2.0†	143.2	83.9	28.0	8.9	20.2	2.2	69.8	222	36.3	20.0	16.3	500 ml. blood 11/8; 50 gm. human serum albumin 11/9; 1,000 ml. ⅙ molar lactate 11/9; 1,500 ml. 10 % dext./H_2O 11/8–11/9; 1,100 ml. stool, 960 ml. vomitus 11/8–11/9; no oral fluid
11/13‡	7.44	.33	23.8	13.4	8.5	64	10.0	47.4	39	129.3	2.4	3.9	2.0†	137.6	75.6	26.0	9.6	24.1	2.3	64.2	176	37.1	25.1	12.0	500 ml. blood 11/10, 1,550 ml. 20 % dext./H_2O 11/11–11/12, 1,500 ml. 10 % dext./sal. 11/11–11/12; 150 gm. human serum albumin, 1,500 ml. 10 % dext./sal., 700 + ml. stool, 2,500 ml. vomitus 11/10–11/12; no oral fluid

Clinical diagnosis: Hodgkin's disease. Oliguria following transfusion reaction. For explanation of superscripts see Table VI.

TABLE IX
CASE IV

Date 1950	pH_s	Vc	$(CO_2)_b$* mM/L.	O_2 cap. Vol. %	O_2 cont. Vol. %	O_2 sat. %	Hb gm. %	$(B_B^-)_b$* mEq./L.	P_{CO_2} mm.	$(Na^+)_s$ mEq./L.	$(K^+)_s$ mEq./L.	$(Ca^{++})_s$ mEq./L.	$(Mg^{++})_s$ mEq./L.	$(B^+)_s$ mEq./L.	$(Cl^-)_s$ mEq./L.	$(HCO_3^-)_s$ mEq./L.	$(Pr^-)_s$ mEq./L.	$(X^-)_s$ mEq./L.	$(HPO_4^=)_s$ mEq./L.	$(Cl^-)_b$ mEq./L.	NPN mg. %	Total Serum Protein gm./L.	Serum Albumin gm./L.	Serum Globulin gm./L.	Remarks
3/10	7.36‡	.13‡	18.2‡	....	....	60†	....	36.7	34.0‡	134.1‡	5.6‡	4.5‡	2.0†‡	146.2‡	99.4‡	18.5‡	11.7‡	14.2‡	2.4‡	....	223‡	50.5‡	24.3‡	26.2‡	1,000 ml. 10 % dext./sal. 3/9
3/11	7.40†	.15†	17.6	6.8	6.6	97	5.1	37.8	29.0	.....	...	...	...	.....	.....	17.7†	....	....	...	....	...	....	....	....	500 ml. blood 3/10
3/15	7.38‡	.19	17.7	8.7	8.4	96	6.5	38.0	31.0	136.8	5.1	4.1	2.0†	148.0	96.8	17.5	....	....	3.4	....	188	....	....	....	500 ml. blood 3/13
3/27	7.33	.27	14.2	12.9	12.3	95	9.7	35.0	28.5	139.3	5.5	4.2	2.0†	151.0	104.7	14.5	13.4	14.3	4.1	....	135	57.5	31.5	26.0	1,500 ml. blood 3/15–3/20
4/4	7.35	.29	12.2	12.4	11.5	93	9.2	35.0	24.0	.....	...	...	...	.....	.....	13.0	....	....	...	....	...	....	.....	....	6,000 ml. 10 % dext./H_2O, 3/31–4/3; 2,000 ml. 5 % dext./H_2O, 4/2; 400 ml. 10 % dext./sal. 4/1
4/7	7.37	.25	18.6	10.4	10.6	101	7.8	40.0	34.0	131.1	3.7	4.0	2.0†	140.8	94.0	19.5	13.5	10.4	3.4	83.6	128	57.3	30.8	26.5	1,000 ml. 5 % dext./sal., 4/4; 1,000 ml. 5 % dext./H_2O, 4/4; 500 ml. ⅙ molar lactate 4/5
4/10	7.36	.24	17.9	10.1	9.7	96	7.5	39.0	34.0	134.4	3.6	4.1	2.0†	144.1	98.6	18.5	12.6	11.5	2.9	89.6	103	53.4	28.9	24.5	1,000 ml. 10 % dext./sal. 4/7; 1,000 ml. ⅙ molar lactate 4/8; 1,000 ml. 5 % dext./sal. 4/9
7/10	7.37	.30	12.8	....	....	95†	....	35.6	24.0	.....	...	...	...	.....	.....	13.5	....	....	...	....	...	....	....	....	1,500 ml. blood 7/6–7/8
7/12	7.38	.34	11.8	14.3	13.3	93	10.7	36.0	22.6	135.2	5.3	4.4	2.0†	146.9	103.2	13.0	15.9	11.2	3.6	92.4	139	66.1	38.3	27.8	1,000 ml. blood 7/10–7/11
12/27	7.38	.32	13.2	13.7	12.9	94	10.3	37.0	25.0	128.8	3.8	5.0	2.0†	139.6	102.9	14.5	13.3	5.4	3.5	86.0	129	51.5	28.5	23.0	950 ml. blood 12/24–12/25
1/3/51	7.38	.35	19.8	15.1	13.8	92	11.3	44.0	37.0	136.8	4.7	5.2	2.0†	148.7	94.4	21.5	13.0	16.6	3.2	79.4	144	51.8	35.4	16.7	1,000 ml. blood 12/27–12/28; 1,000 ml. 5 % dext./H_2O 12/27; 200 ml. normal saline 12/28; 1,000 ml. ⅙ molar lactate 12/28

Clinical diagnosis: Chronic pyelonephritis; uremia. For explanation of superscripts see Table VI.

used to calculate the moiety of the whole blood buffer base contributed by the serum proteins, $B^+(Pr^-)_b$. The base bound by the hemoglobin of the whole blood, $B^+(Hb)_b$, was taken as the difference between the whole blood buffer base, $(B_B{}^+)_b$, and the sum of the base bound by bicarbonate, $B(HCO_3^-)_b$, the serum inorganic phosphate, $B^+(HPO_4^=)_b$, and the base bound by the serum proteins, $B(Pr^-)_b$, all expressed per liter of whole blood. The base bound by the inorganic phosphate of the whole blood, $B^+(HPO_4^=)_b$, was assumed to be the sum of the base bound by the inorganic phosphate of the serum, $(HPO_4^=)_s$, and that of the red blood cell, $(HPO_4^=)_c$, assuming the latter to be equal in its concentration to that in the serum. As the concentration of the serum inorganic phosphate was only slightly elevated in the cases reported herein, any addition to the buffer capacity of the red blood cells was due to an increase in organic acid-soluble phosphorus, Guest and Rapoport.[31]

The calculations used in the distribution of the ions between the serum and the red blood cells: The concentration of the chloride, $(Cl^-)_s$, of the red blood cells was calculated by the method of Hald and Eisenman[32] using the whole blood chloride $(Cl^-)_b$, the serum chloride $(Cl^-)_s$, and the hematocrit. The red blood cell bicarbonate concentration, $(HCO_3^-)_c$, was calculated from the whole blood bicarbonate concentration, $(HCO_3^-)_b$, as calculated previously and the serum bicarbonate concentration, $(HCO_3^-)_s$, in a manner similar to the procedure used to calculate the red cell chloride concentration, $(Cl^-)_s$, as given previously. The concentration of the undetermined anions of the serum, $(X^-)_s$, was calculated as the difference between the sum of the total cations, $(Na^+)_s$, $(K^+)_s$, $(Ca^{++})_s$ and $(Mg^{++})_s$, and the determined and calculated anions, $(Cl^-)_s$, $(HCO_3^-)_s$, $(HPO_4^=)_s$ and $(Pr^-)_s$. The concentrations of the undetermined anions, $(X^-)_c$, and inorganic phosphate, $(HPO_4^=)_c$, of the red cells were assumed equal to their respective concentrations in the serum, $(X^-)_s$ and $(HPO_4^=)_s$. The anion equivalency of the hemoglobin of the red blood cells, $(Hb^-)_c$, was calculated from the hematocrit, Vc, the concentration of the oxygenated and reduced hemoglobin per liter of whole blood and the base bound by each of these at the given pH, using the data given in Table IV of Singer and Hastings.[3] The base bound by the serum proteins, $(Pr^-)_s$, was calculated from the data as

TABLE X
CASE V

Date 1951	pH$_s$	Vc	$(CO_2)_b$* mM/L.	O_2 cap. Vol. %	O_2 cont. Vol. %	O_2 sat. %	Hb gm. %	$(B_B{}^+)_b$* mEq./L.	P_{CO_2} mm.	$(Na^+)_s$ mEq./L.	$(K^+)_s$ mEq./L.	$(Ca^{++})_s$ mEq./L.	$(Mg^{++})_s$ mEq./L.	$(B^+)_s$ mEq./L.	$(Cl^-)_s$ mEq./L.	$(HCO_3^-)_s$ mEq./L.	$(Pr^-)_s$ mEq./L.	$(X^-)_s$ mEq./L.	$(HPO_4^=)_s$ mEq./L.	$(Cl^-)_b$ mEq./L.	NPN mg. %	Total Serum Protein gm./L.	Serum Albumin gm./L.	Serum Globulin gm./L.	Remarks
2/7	7.41	.43	31.7	17.7	12.9	72.7	13.2	57.3	58	133.2‡	4.1‡	4.6‡	1.5‡	143.4‡	88.9	36.3	16.3‡	0.3	1.6‡	69.2	27	70.2‡	30.6‡	39.6‡	Cyanosis, dyspnea, orthopnea, cough, edema of lower legs and feet; coarse rales at lung bases
2/12	7.39	.50	39.1	19.9	18.3	92.0	14.8	66.0	76	135.2	5.2	5.4	1.8	147.6	78.5	45.3	16.2	5.9	1.7	62.0	25	71.8	32.1	39.7	In O_2 tent since 2/7 except for meals; cough improved, less dyspnea, no edema, coarse rhonchi at lung bases; slightly cyanotic; blood samples obtained with patient in tent breathing 52% O_2
2/26	7.47	.45	30.8	18.5	14.1	76.2	13.8	58.0	52	135.8‡	4.5‡	5.0‡	1.7‡	147.0	89.6	36.3	16.2‡	2.8	2.1‡	69.6‡	23‡	68.1‡	30.9‡	37.2‡	Out of O_2 tent for past 7 days except at night; respirations not labored but still dyspneic; coughing; cyanosis persists

Clinical diagnosis: Pulmonary fibrosis and emphysema. Chronic asthmatic bronchitis. Arteriosclerotic heart disease and cor pulmonale. For explanation of superscripts see Table VI.

TABLE XI

CASE VI

Date 1950	pH_a	Vc	$(CO_2)_b$* mM/L.	O_2 cap. Vol. %	O_2 cont. Vol. %	C_2 sat. %	Hb gm. %	$(B_B{}^+)_b$* mEq /L.	PCO_2 mm.	$(Na^+)_a$ mEq. /L.	$(K^+)_a$ mEq. /L.	$(Ca^{++})_a$ mEq. /L.	$(Mg^{++})_a$ mEq./L.	$B(^+)_a$ mEq. /L.	$(Cl^-)_a$ mEq. /L.	$(HCO_3{}^-)_a$ mEq./L.	$(Pr^-)_a$ mEq. /L.	$(X^-)_a$ mEq. /L.	$(HPO_4{}^=)_a$ mEq./L.	$(Cl^-)_b$ mEq. /L.	NPN mg. %	Total Serum Protein gm./L.	Serum Albumin gm./L.	Serum Globulin gm./L.	Remarks
7/3	7.42	.35	41.8	15.7	15.2	96	11.7	67.0	74	.....	...	...	...	.....	....	46.0	....	...	...	....	..	....	....	....	In O_2 tent for previous five days, not cyanotic; arterial puncture while in O_2 tent (38% O_2); drowsy and confused
7/6	7.52	.34	27.9	15.2	13.4	88	11.3	53.8	38	.....	...	...	...	.....	....	30.4	....	...	...	....	..	....	....	....	Out of O_2 tent for two hours before and during arterial puncture; no obvious cyanosis; slightly improved; sensorium clear
7/7	7.48	.33	29.2	15.8	14.9	95	11.8	55.0	44	.....	...	...	...	.....	....	32.4	....	...	...	....	..	....	....	....	In O_2 tent except for meals for past 24 hr.; arterial puncture while in tent (51% O_2); sensorium clear
11/14	7.42	.42	28.1	19.2	15.1	79	14.3	53.9	49	.....	...	...	...	.....	....	32.0	....	...	...	....	..	....	....	....	Intermittent nasal O_2 therapy for previous ten days; none in previous 12 hr.; sensorium clear; audible wheezing; slight cyanosis
11/15	7.39	.43	28.4	19.0	18.4	97	14.2	54.0	56	.....	...	...	...	.....	.....	32.6	....	...	...	....	..	....	....	....	Placed in O_2 tent (38% O_2) 10 min. before arterial puncture; respirations labored, 30/min., no cyanosis; sensorium clear
11/16	7.38	.41	30.1	18.2	17.8	98	13.6	55.4	59	.....	...	...	...	.....	....	34.4	....	...	...	....	..	....	....	....	In O_2 tent for previous 24 hr. except for meals; condition improved; arterial puncture while in O_2 tent (40% O_2); sensorium clear
11/17	7.36	.40	30.5	18.9	17.8	94	14.1	55.0	62	140.9	4.5	4.8	2.0†	152.2	94.4	34.5	16.1	4.8	2.4	76.4	27	66.1	41.6	24.5	In O_2 tent for previous 48 hr. except for meals; feels much improved; sensorium clear; respirations still labored; arterial puncture while in O_2 tent (40% O_2)

Clinical diagnosis: Pulmonary fibrosis, emphysema, asthmatic bronchitis. For explanation of superscripts see Table VI.

given by Van Slyke et al.[10] In these ionic representations (X−) includes the undetermined anions as calculated previously and the inorganic phosphate. When whole blood chloride was not available, the distribution of chloride between red cells and serum was derived from the calculated concentration of water of the serum according to the data of Eisenman et al.,[33] the distribution ratios of chloride between cells and serum, and the distribution ratios of bicarbonate between cells and serum as given by Dill et al.[9]

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Seminars on Gastrointestinal Physiology

Neural Regulation of Gastric and Intestinal Motility*

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THE gastrointestinal tract displays several types of motility which generally are classified under the headings of peristalsis, rhythmic contractions and tonus.[1] Each of these types of motility is present in the stomach and small bowel, in varying degrees, in the absence of extrinsic nerves; hence the extrinsic nerves are concerned with the regulation rather than the initiation of motor functions. In general, the extrinsic nerves serve to increase or to decrease the motor responses of the bowel to stimuli within the lumen. In experimental animals and sometimes in man the stomach below the level of the cardia and the small bowel can function adequately under ordinary conditions in the absence of extrinsic innervation. However, dispensability is an exceedingly crude index of utility. Extrinsic denervation of the stomach or intestine is followed by changes in the basal level of motility, loss of reflexes, altered responsiveness to drugs and alterations in the symptomatology of diseases involving abdominal organs.

INNERVATION AND TYPES OF DENERVATION

The stomach and upper small intestine are innervated by each of the two divisions of the autonomic system. The parasympathetic supply is by the vagus nerves and the sympathetic supply is by the major and minor splanchnic nerves and connections from the lumbar sympathetic chains. The vagal fibers are preganglionic, and they synapse with neurons of the intrinsic plexuses of the stomach and small intestine. The preganglionic fibers of the sympathetic system synapse with cell bodies in the preaortic ganglia, mainly the celiac ganglia, and postganglionic fibers pass from these cell bodies to innervate directly the smooth muscle of the stomach and small intestine. (For further details and discussion of disputed points see books by Kuntz.[2,3]) (Figs. 1 and 2.)

Vagal Denervation. The stomach and small intestine can be deprived of most of their vagal innervation by sectioning the nerves at the level of the diaphragm. This is a preganglionic denervation; postganglionic vagal denervation is not possible since the second neuron in the vagal pathway is intrinsic. The question of producing a "chemical" postganglionic vagal denervation by means of anticholinergic drugs such as atropine deserves comment. That atropine does not exert its actions only by blocking the effects of impulses arriving by the vagus is shown by the fact that this drug is just as inhibitory to the vagally denervated intestine as to the innervated.[4] Also, anticholinesterase compounds such as eserine have as much stimulant action on the vagally denervated intestine as on the normal.[5] Moreover, as will be considered subsequently, the vagus to the gastrointestinal tract is a mixed nerve; some of the fibers exert inhibitory effects and some exert excitatory effects. It seems probable, in view of the direct effects of epinephrine and acetylcholine upon intestinal smooth muscle, that the fibers having an excitant effect (except to the pyloric sphincter) are cholinergic and those having an inhibitory effect are adrenergic. Larger doses of atropine than those used in man are required to block the excitatory effect on gastric motility produced by vagal stimulation,[6] and any adrenergic postganglionic fibers in the

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vagus would not be blocked. From these facts it is quite apparent that the effects of atropinization on gastric or intestinal motility cannot be interpreted as being identical to or even similar to those which are caused by vagotomy.

doses of atropine which do not block the effects of vagal stimulation on gastrointestinal motility do have a depressant influence on motility and interfere with the stimulant action of acetylcholine brought to the intestine by the blood

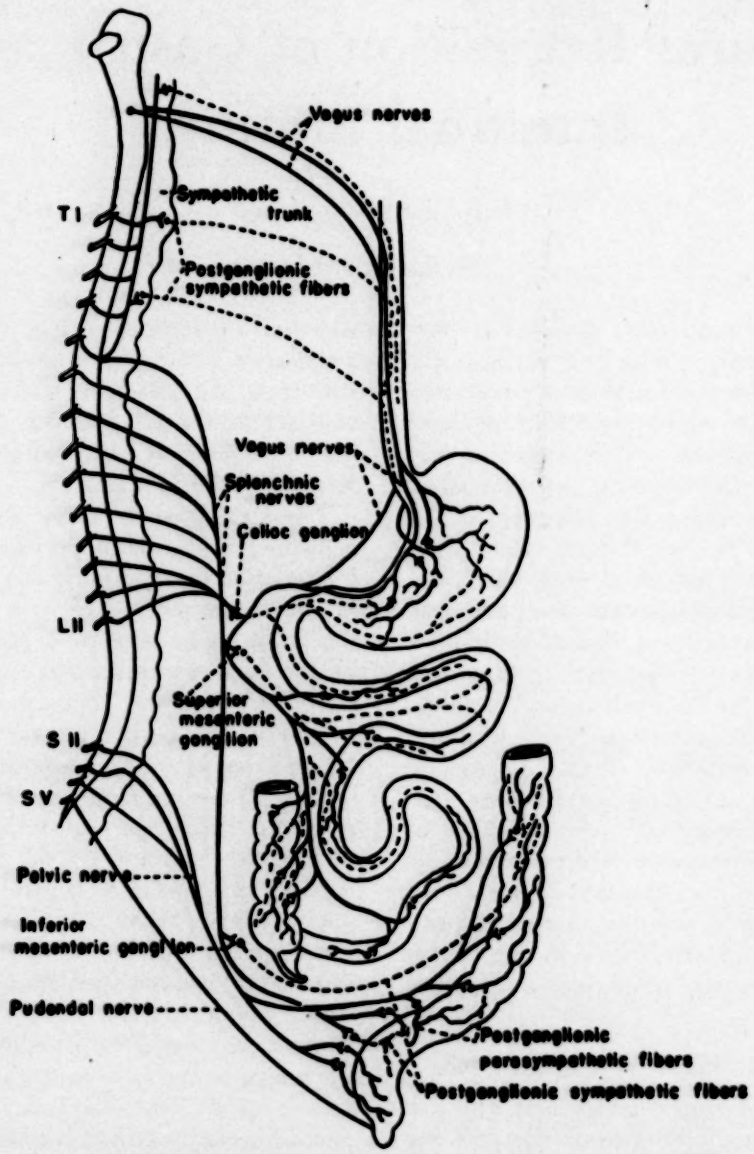

FIG. 1. Diagram illustrating the sympathetic and the parasympathetic nerves of the digestive tract and the pudendal nerve to the anal sphincter. (From Kuntz. Visceral Innervation and Its Relation to Personality Springfield, Ill., 1951. Charles C Thomas.)

The dose of atropine needed to produce cholinergic blockade is very low at some neuroeffector junctions, such as in the salivary glands and gastric glands, but the dosage required to block the effects of vagal stimulation on gastrointestinal motility is much greater and is above that which is feasible for therapy.[7] However,

stream.[4] A probable explanation for these facts will be presented later.

Sympathetic Denervation. Preganglionic sympathetic denervation of the stomach and intestine can be accomplished by bilateral section of the major and minor splanchnic nerves and removal of the lumbar sympathetic chains. The sympa-

thetic denervation of the intestine is not complete unless the latter procedure is included. Postganglionic sympathetic denervation can be achieved by removal of the celiac and other preaortic ganglia. In experimental animals the postganglionic denervation has considerably parts. In addition, however, the efferent pathways to the bowel may be activated on a reflex basis by afferent influences arising elsewhere than in the bowel, or they may be activated by impulses originating in the hypothalamus or cerebral cortex.

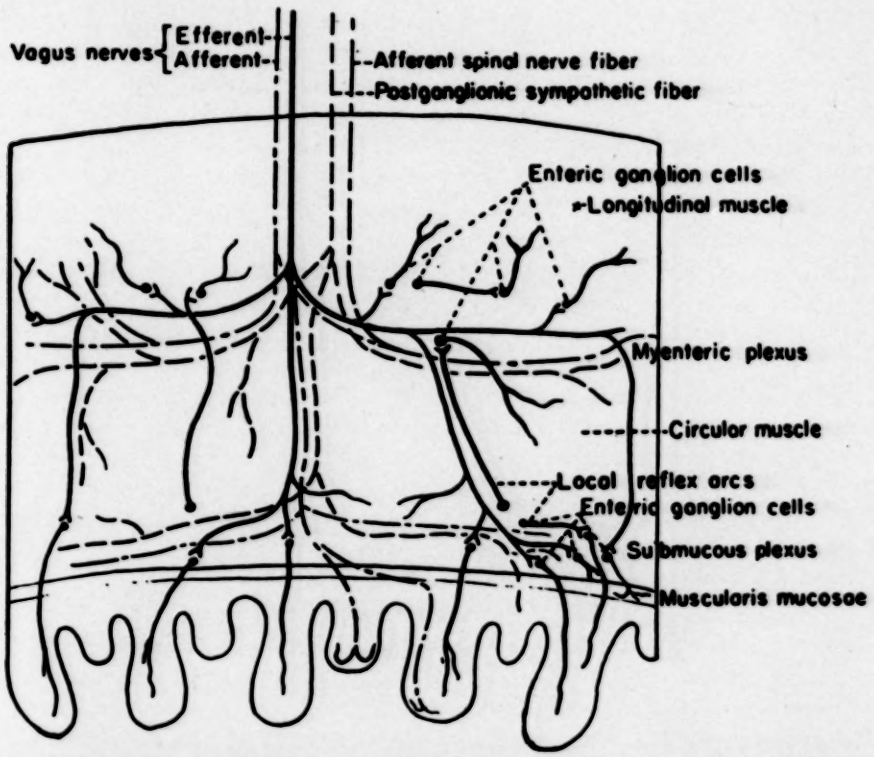

FIG. 2. Diagrammatic illustration of the arrangement of nerve cells and nerve fibers in the intramural plexuses in the intestine. (From Kuntz. Visceral Innervation and Its Relation to Personality. Springfield, Ill., 1951. Charles C Thomas.)

more serious effects than the preganglionic.[8] Whether this is related to trophic influences in the bowel or to the greater sensitization to epinephrine and other substances[9] or to some entirely different mechanisms is not known. It is questionable whether any true reflexes controlling gastrointestinal motility are mediated through the preaortic ganglia after the ganglia have been deprived of their connections with the central nervous system.[10] Reflexes concerned with control of gastrointestinal motility are mediated either by the intrinsic ganglia or through arcs which involve the spinal cord or the vagal center in the medulla. The former are called intrinsic reflexes and the latter are known as extrinsic or long reflexes. Clearly, the principal function of the extrinsic nerves to the bowel, as far as motility is concerned, is to influence the activity in a given part of the bowel on the basis of changing conditions locally and in other

EFFECTS PRODUCED BY STIMULATION OF EXTRINSIC NERVES

Attempts to learn the utility of visceral efferent nerves simply by observing changes in activity of an organ following either sectioning or electrical stimulation of the nerve in acute experiments frequently are not rewarding and may be misleading. Sectioning of a nerve produces negligible effects unless the nerve is "tonically" active; and, furthermore, the degree of activity at the time may not be the normal state but may be an artefact of abnormal conditions created in the experiment. Also, some agents used for anesthesia have a blocking or reversing action on the effects of neural stimulation.[11,12] In view of these facts it must be considered that relatively little is known about the normal basal level of activity in many of the efferent nerves supplying thoracic and abdominal viscera.

When one is dealing with a mixed nerve, either sectioning or stimulating the nerve reveals at best the predominant or prepotent type of fiber rather than all of the types which are present. More subtle methods are necessary if the physiologic roles subserved by visceral nerves are to be clarified. For example, the sectioning of dorsal roots of spinal nerves will cause loss of certain somatic reflexes but this may not be evident if one does not attempt to elicit the reflex. Also, direct stimulation of the central end of a sectioned dorsal root regularly will elicit a flexor reflex; nevertheless, afferent fibers for extensor reflexes are contained in this root. The presence of the latter fibers, which physiologically are fully as important as the former, might never be detected by studies involving direct stimulation. Nevertheless, it is necessary to consider the effects of stimulation or denervation even though the interpretations must be guarded.

Direct Stimulation of the Vagi. From numerous experiments the fact emerges that either increased motility or decreased motility of the stomach and intestine can be produced by direct stimulation of the peripheral end of the vagus nerve sectioned below the level of the branches to the heart.[13–18] It does not seem profitable in the light of present information to analyze in detail the conditions under which inhibition rather than stimulation of motility is obtained. It is evident, of course, that no inhibition of motility can be demonstrated when the bowel is already quiescent, and that excitation cannot be demonstrated when the motility is maximal. If some vagal preganglionic fibers innervate cholinergic neurons and some innervate adrenergic neurons in the ganglionated plexuses of the stomach and small intestine, variable effects from direct stimulation of the vagus would be predicted. Not all cholinergic postganglionic neurons are contained in the craniosacral system and it is true also that not all adrenergic postganglionic neurons are contained in the thoracolumbar system. Although variable results are obtained, the typical effect of prolonged stimulation of vagal branches to the stomach and intestine is an increase in tonus and motility. It is quite common for inhibition to occur initially, and this is replaced by excitation as the stimulation is prolonged. Stimulation of adrenergic pathways to the bowel or continuous injection of moderate amounts of epinephrine do not cause sustained inhibition; hence, if the cholinergic nerves are capable of exerting sustained effects, the response of the stomach and intestine which is commonly seen during direct stimulation of the vagus is what one would expect if both adrenergic and cholinergic intrinsic neurons are activated. When the stomach and intestine are perfused during vagal stimulation, there is an increase in the amount of acetylcholine entering the perfusate,[19,20] and the excitatory effects on the stomach produced by vagal stimulation are enhanced by eserine and abolished by atropine.[21]

Indirect Stimulation of Excitatory Vagal Pathways. Vagal excitatory pathways to the stomach appear to be selectively activated following injection of insulin; both motility[22] and secretion[23] are increased. In the fasting individual who is not exhibiting hunger contractions the appearance of such contractions may be induced; or if hunger contractions are already present, frequency and amplitude are increased. The production of acute erosive gastritis following large doses of insulin has been reported.[24] Failure to cause an increase in secretion of gastric juice by injection of insulin has been used as an index for completeness of vagotomy,[23] and it is true also that gastric motility is not stimulated by insulin after vagotomy. Actually, an inhibition of motility of the stomach, which does not appear to be related to action of epinephrine or of adrenergic neurohormones, is produced by insulin in vagotomized dogs.[25]

The actions of anticholinesterase compounds cannot be viewed as resulting only from potentiation of the vagus. The synthesis of acetylcholine, especially in the small intestine, occurs at a relatively rapid rate in the absence of any extrinsic nerves to the bowel, and anticholinesterases protect the locally produced acetylcholine.

Stimulation of Sympathetic Nerves. The effects on gastrointestinal motility produced by stimulation of the sympathetic supply to the stomach and intestine are more consistent than those produced by vagal stimulation.[14,15,26–28] Usually the wall of the stomach and small intestine become atonic and all types of motility decrease or cease, while the pyloric sphincter may show an increase in tonus. However, the inhibiting effects of sympathetic stimulation tend to wear off rather rapidly so that tonus and motility may be regained even though stimulation is maintained. This "break through" is related to development of refractoriness of the musculature to the effects of the chemical mediator, epinephrine or norepinephrine, rather than to

failure of production of the mediator at the adrenergic neuroeffector junctions. A similar "break through" occurs within a few minutes during injection of epinephrine or related compounds at a constant rate.[29] Characteristically, when the sympathetic stimulation is terminated, there is a period of hypermotility of the intestine before the return to the control level of activity.

It is possible to obtain excitatory effects on the stomach from stimulation of the sympathetic supply and when these effects are produced they are enhanced by eserine and abolished by atropine.[21] Also, different responses are obtained with different rates of stimulation or different duration of currents applied to the sympathetic trunk or to the mesenteric nerves.[27,28]

If the splanchnic nerve is stimulated while the adrenal glands remain intact, a part of the intestinal inhibition, after a latent period of fifteen to twenty seconds, very likely is produced by epinephrine liberated from the adrenal medulla. However, the effect of splanchnic stimulation still is observed in the absence of the adrenal glands and the latent period from the beginning of stimulation to the onset of inhibition may be as short as one or two seconds. Hence blood-borne substances cannot be responsible for the initial inhibitory effects produced by stimulation of the sympathetic nerves to the bowel. If a segment of intestine is perfused during stimulation of the mesenteric nerve supplying it, a substance which has an inhibitory action on intestinal motility enters the perfusate.[29]

The results of studies involving direct stimulation of the extrinsic nerves may be summarized by the following statement from Thomas:[30] "It is more in accord with the facts to consider both nerves, not as motor or inhibitory to the visceral muscle, but as comprising dual pathways for nerve impulses from the central nervous system which serve to modify the reactivity of the local neuromuscular mechanism so that it reacts in a manner appropriate to the stimuli present."

EFFECTS OF EPINEPHRINE AND ACETYLCHOLINE

A question which is more specific than that of the effects on motility produced by direct stimulation of extrinsic nerves to the intestine is whether a given chemical mediator of nerve impulses may have a qualitatively different effect on the same smooth muscle cell when the cell is relaxed than when it is contracted. A concept which seems acceptable at present is that smooth muscle cells are of two main types. Smooth muscle containing the E type of receptive mechanism, according to Cannon's terminology,[31] is caused to contract by epinephrine, and smooth muscle containing the I type of receptive mechanism is relaxed by epinephrine. Acetylcholine has an effect opposite to that of epinephrine on dually innervated smooth muscle cells. The muscle in the wall of the stomach and intestine is of the I type—inhibited by epinephrine and contracted by acetylcholine.[32–35] (Fig. 3.) Evidently, some of the E type of muscle is found in the pyloric sphincter. A good example of the E type of muscle is that in the arterioles of the skin of the hands and feet; these vessels are constricted by epinephrine and dilated by acetylcholine. In studies of effects of epinephrine injected intravenously at a constant rate into unanesthetized dogs no dose was found which would cause an increase in intestinal motility.[9,35] It was noted, however, that a phase of hypermotility commonly follows the cessation of the injection, as is seen following a period of inhibition produced by stimulation of the sympathetic pathway to the intestine.[15,29] Occasional reports of excitation of the intestine by epinephrine are probably based on observations of this hypermotile recovery phase. A simple, probable explanation of the results is that epinephrine itself always has an inhibitory effect, in physiologic ranges, and that as the effect of the epinephrine wears off a hyperactive recovery phase ensues.

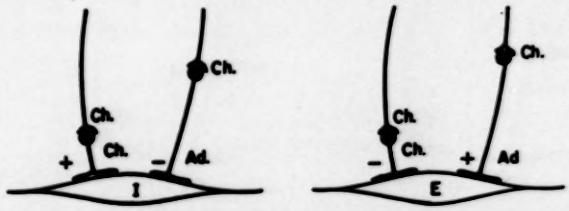

FIG. 3. Diagram of innervation of two major types of smooth muscle cells classified on basis of effects of epinephrine and acetylcholine. In each of the two diagrams the parasympathetic innervation is shown on the left and the sympathetic innervation on the right. The "I" type of smooth muscle is inhibited by epinephrine and stimulated by acetylcholine; the "E" type is stimulated by epinephrine and inhibited by acetylcholine. E and I designate the two types of "receptive mechanisms" which must be postulated to explain the fact that a single substance, e.g., epinephrine, causes one cell to relax and the other to contract. The direction of the influences of the chemical mediators is determined by the type of receptive mechanism and not by the anatomic source of the nerve fibers.

The direct effects of acetylcholine on intes-

tinal motility cannot be determined following an intravenous injection into an intact animal and this compound cannot be used as a therapeutic agent to stimulate the stomach or intestine. The intestine does develop a brief spasm effect when applied directly to intestinal smooth muscle; however, it also has a stimulatory effect on the intrinsic ganglion cells most of which are cholinergic but some of which possibly are adrenergic.

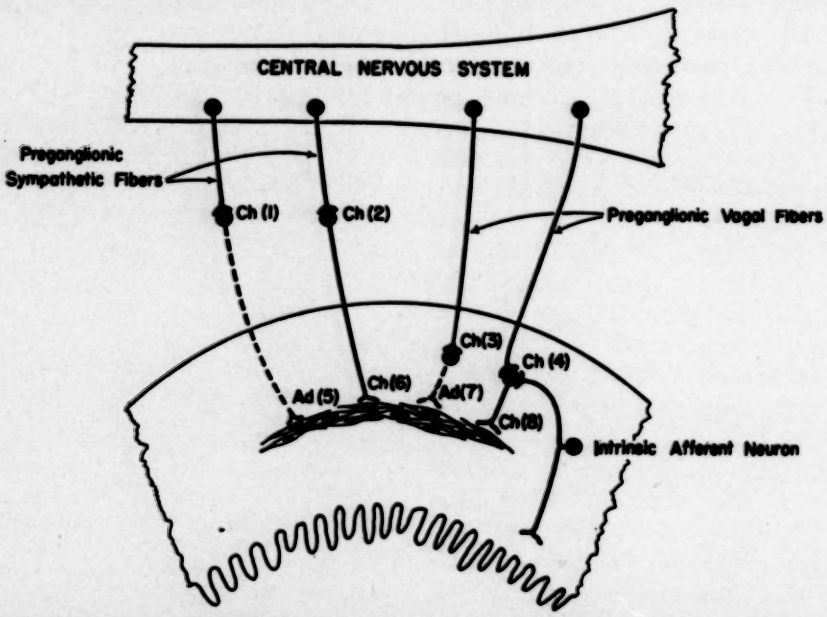

FIG. 4. Diagram illustrating the innervation of smooth muscle of the gastric and intestinal wall. This muscle is of the "I" type; it is inhibited by epinephrine and stimulated by acetylcholine. The preganglionic neurons of both the sympathetic and parasympathetic systems (No. 1, 2, 3 and 4) are cholinergic. Both the sympathetic and the vagal preganglionic fibers innervate adrenergic and cholinergic neurons (No. 5, 6, 7 and 8). Intrinsic cholinergic neurons (No. 8) innervated by preganglionic vagal fibers probably are innervated also by intrinsic afferent neurons. (Modified from Youmans. Nervous and Neurohumoral Regulation of Intestinal Motility. New York, 1949. Interscience Publishers.)

as the first response following an intravenous injection of acetylcholine.[36] This lasts for only a few seconds; and then epinephrine, most of which is reflexly liberated during the severe arterial hypotension occurring secondary to ventricular asystole, produces a period of amotility. If doses of acetylcholine are given which do not have the cardioinhibitory and hypotensive effects, no significant effect on intestinal motility is seen. This is understandable in view of the fact that acetylcholine is destroyed quite rapidly by blood, and the circulation time to the intestine is approximately two times that to the heart.

Epinephrine has a direct inhibitory effect on the longitudinal and circular muscular layers of the small intestine. The degree and duration of the inhibition is related to the concentration of epinephrine and to the level of tonus and motility of the intestine at the time of application of the epinephrine. Acetylcholine has an excitatory

The actions of norepinephrine on the intestine are qualitatively indistinguishable from those of epinephrine; furthermore, there is a negligible difference in the relative potency of these two compounds as inhibitors of intestinal motility.[35] It is possible that norepinephrine as well as epinephrine is liberated as a mediator by the adrenergic neurons of the gastric and intestinal wall; but in view of their similar actions the question of which is liberated is academic.

The conclusion from the studies concerning the effects produced by stimulating the extrinsic nerves and the effects exerted by the chemical mediators themselves is that inhibitory influences to the wall of the stomach and the intestine are mediated on the efferent side, postganglionically, by adrenergic neurons and the excitatory influences are mediated by cholinergic neurons. Most or all of the preganglionic neurons in both the sympathetic system and parasympathetic system are cholinergic. (Fig. 4.) Adrenergic and

cholinergic postganglionic neurons are present in each system but adrenergic fibers predominate in the sympathetic system. When the bowel is influenced reflexly, a specific type of postganglionic neuron is selectively activated through integrative mechanisms in the central nervous system. Adrenergic postganglionic neurons are utilized for the inhibitory influences and cholinergic neurons for excitatory influences. Evidence to be presented indicates that reflex inhibition of the stomach can be mediated on the efferent side by either vagal or sympathetic pathways or perhaps by both simultaneously.

EFFECTS FOLLOWING SECTIONING OF EXTRINSIC NERVES

When nerves to the bowel are sectioned surgically, usually the purpose is to eliminate one or two specific actions. For example, the object may be to prevent neural vasoconstrictor influences in the abdominal viscera in patients with arterial hypertension. The question then arises concerning what ill effects will be produced by the elimination of the other functions of the nerves. When the sympathetic nerves are sectioned, one would look for changes related to the elimination of pain and to loss of the reflexes which normally are elicited by intestinal distention or pressure. The loss of reflexes does not seem to be disabling. The change in symptomatology produced by pathologic conditions in the stomach and small bowel may be considerable. Pain pathways activated by intestinal distention[37,38] and afferent fibers from the visceral peritoneum[39] are found largely or exclusively in the thoracolumbar afferent system. The ill effects of vagal section, on the other hand, are related almost entirely to the decrease in gastric tonus and impairment of gastric emptying.

Effects of Sympathectomy. Operative procedures which result in complete or nearly complete sympathetic denervation of the stomach and small intestine have been performed in relatively large numbers of patients. Gastrointestinal disturbances are not prominent as sequelae of these procedures,[40–42] hence it appears that bowel functions of all types are performed reasonably well in the absence of the sympathetic innervation. In most instances the sympathectomies have been predominantly preganglionic. There is some indication that motility is moderately increased following sympathectomy.[43–45]

In dogs no ill effects are observed following a preganglionic sympathetic denervation of the intestine, especially if the two sides are done in separate operations.[8] However, a high mortality rate occurs following removal of the celiac ganglia in dogs. Bloody diarrhea usually develops and ulceration of the stomach and upper part of the small intestine has been reported.

Effects of Vagotomy. In recent years vagotomy at the level of the diaphragm has been performed in large numbers of patients for the treatment of recurrent peptic ulcers. From studies on some of these patients it has become evident that prominent, prolonged effects on gastric motility are produced by vagotomy.[46–52] Many of the patients develop atony and dilatation of the stomach. In some cases considerable recovery of tonus and motility occur after a few weeks but in others the impairment of gastric emptying persists. The ill effects on emptying are sufficiently frequent and persistent so that a gastroenterostomy or pyloroplasty is combined with vagotomy for the treatment of peptic ulcer. As would be expected, the gastric musculature is still responsive to choline derivatives after vagotomy, and carbaminoyl betamethylcholine (urecholine®) has been found to be useful as a part of the regimen for treatment of gastric dilatation occurring as a complication following vagotomy. McCrea et al.[53] minimized the effects of vagotomy in dogs but others have observed effects in dogs[54,55] and monkeys[56] similar to those seen in man.

Dogs die of malnutrition if the vagi are sectioned at the mid-cervical level but their nutrition is not seriously affected by vagotomy at the level of the diaphragm. It is of interest that the relaxation of the cardia which occurs in advance of a peristaltic wave in the lower esophagus is not prevented by cutting both vagi at the lower esophageal level but is prevented if, in addition to vagotomy, the esophagus is encircled with an incision which is carried down to the submucosa after which the sectioned layers are anastomosed.[57] Dogs which were subjected to both vagotomy and cutting of all layers of the esophagus except the mucosa and submucosa experienced considerable dysphagia. Thus it is indicated that, in dogs, the stomach below the level of the cardia can carry on its essential function in the absence of any vagal innervation and that the cervical vagotomy is fatal because of esophageal weakness or paraly-

sis combined with cardiospasm. The effects of vagotomy at the cervical level are not as serious in cats and monkeys as in dogs and rabbits[58,59] since the lower part of the esophagus regains motility in the former species but not in the latter.

Effects of Vagotomy and Sympathectomy. In dogs usually no serious effects are produced by bilateral preganglionic sympathectomy and bilateral vagotomy at the level of the diaphragm when the denervation is done in three stages.[8] The animals tolerate these procedures well; they eat normally and maintain their weight.

In a few patients both vagotomy and sectioning of most of the sympathetic pathways to the upper abdominal region have been performed.[60] The combination of these procedures is tolerated if a gastroenterostomy is made at the time of vagotomy. However, the symptomatology of abdominal conditions is greatly altered. Perforation of an ulcer in such a patient did not cause any immediate symptoms.[60]

Effects of Ganglionic Blockade with Tetraethyl Ammonium Compounds. Tetraethyl ammonium chloride or bromide will block the transmission of impulses in both sympathetic and parasympathetic autonomic ganglia. Most of its effects following systemic administration are attributable to the ganglionic blockade. The injection of tetraethyl ammonium chloride in sufficient amounts would be expected to produce essentially a chemical preganglionic denervation of the bowel and hence deprive the smooth muscle of any influences reaching it as a result of the activity of the extrinsic nerves. It is to be expected that tetraethyl ammonium chloride might, in addition, impair transmission from intrinsic afferent neurons to the postganglionic cholinergic neurons; and it is possible that it would influence in some degree transmission at the cholinergic neuroeffector junction. Finally, if the fall in arterial blood pressure produced by intravenous injection of tetraethyl ammonium chloride should be very precipitous or very severe epinephrine would be liberated from the adrenal medulla, and this would inhibit gastrointestinal motility.

Although one cannot assume that the effects of tetraethyl ammonium chloride on the intestine are related entirely to the removal of extrinsic neural effects, it is true that most such effects are prevented, hence the changes in motility produced by this compound are of interest. A depressant effect of tetraethyl ammonium ion on gastric and intestinal motility in man has been reported by several groups of investigators.[61–66] In the studies by Dodds et al.[65] cessation of peristalsis in both the stomach and the intestine was noted, the effect on the stomach being more prolonged, and considerable delay in gastric emptying was produced following slow intravenous injection of tetraethyl ammonium chloride. In one patient the blood pressure fell from 118/80 to 50/40 and this reaction was treated by subcutaneous administration of epinephrine. Tetraethyl ammonium chloride causes liberation of epinephrine in patients with pheochromocytoma and in normal animals either reflexly or as a result of a direct action on the adrenal medulla. Brown et al.[63] report reduction in gastric motility and in secretion of gastric juice following injection of tetraethyl ammonium chloride.

Inhibition of intestinal motility has been observed uniformly following administration of tetraethyl ammonium chloride. Posey, Brown and Bargen[66] noted that all forms of activity of the intestine, including rhythmic contractions, disappear after injection of tetraethyl ammonium chloride. They state that their observations lead them to believe that the rhythmic contractions of the intestine are principally neurogenic in origin. However, it is possible that the inhibition observed in the intact subject is related to epinephrine liberation or at least to some action of tetraethyl ammonium chloride other than its ganglionic blocking action. In this connection it should be remembered that atropine, which blocks the cholinergic innervation more peripherally than tetraethyl ammonium chloride, will not prevent rhythmic contractions of the intestine in response to suitable pressure levels in the intestinal lumen; and it does not seem likely that the adrenergic innervation of the intestine, which is inhibitory, is essential for rhythmic contractions. Furthermore, cessation of rhythmic contractions of the intestine does not signify incapability of exhibiting rhythmic contractions; it may occur secondary to loss of tonus in which case the stimulus for rhythmic contractions also is lost. It is probable that the activity of cholinergic neurons in the intestinal wall is essential for the maintenance of normal tonus, and some degree of tonus is necessary in order that a given amount of filling will produce pressure or tension sufficient to elicit rhythmic contractions.

INTRINSIC REFLEXES AND PRODUCTION OF ACETYLCHOLINE

Evidence that intrinsic neurons, and possibly other structures of the intestinal wall, more or less continuously release acetylcholine under physiologic conditions is summarized elsewhere.[10,67] The principal original articles are listed in the bibliography.[68–78] This is an important concept since it necessitates considerable revision of views concerning the mechanism of action on gastrointestinal motility of anticholinesterases and of anticholinergic compounds. If basal production of acetylcholine in the gastrointestinal wall is occurring at a relative high level and stimulation of extrinsic nerves serves only to elevate moderately the rate of production, it can be expected that compounds which influence the production or action of acetylcholine will have an effect on the extrinsically denervated intestine that is not unlike their effects when the extrinsic nerves are intact. That this is true for eserine and atropine was demonstrated by the use of denervated intestinal segments *in situ* in dogs.[4,5] Eserine was found to have a stimulant action and atropine an inhibitory action just as in the case of the innervated segments. The effects on the denervated intestine were as great as on the innervated intestine in the case of eserine and even greater than normal in the case of atropine. It is well known that atropine and eserine exert qualitatively the same actions on isolated intestine as upon the intestine *in situ*, and it has been shown repeatedly that isolated intestine produces acetylcholine. In fact, the intestine produces acetylcholine under any conditions in which the intrinsic neurons of the intestine can be expected to be functional. The amount of acetylcholine produced in the wall of the stomach under a given set of conditions is considerably less than the amount produced by the intestine.

The intestinal wall contains considerable amounts of cholinesterase;[79] and, as indicated by the fact that acetylcholine is liberated from the intestine during stimulation of the vagus,[20] it contains either cholinergic neurons or cholinergically innervated neurons.

Peristalsis is considered to be an intrinsic reflex and it seems probable that it involves, on the efferent side, some of the same intrinsic cholinergic neurons that are innervated by vagal (preganglionic) fibers. It cannot be reasonably doubted that the intrinsic neurons concerned with peristalsis are cholinergic, and a corollary to this interpretation would be that under any conditions which elicit peristalsis acetylcholine is produced in the intestine exclusive of the action of extrinsic neurons. It is well known that the extrinsic nerves may depress or increase peristaltic activity; but peristalsis, as a pattern of motility, is independent of extrinsic nerves.

The normal level of tonus observed in the intestine appears to be dependent in part on the action of acetylcholine produced at a basal level by entirely intrinsic mechanisms. Commonly, changes in rhythmic contractions occur secondary to changes in tonus. Since atropine blocks the response of the intestine to acetylcholine carried to it by the blood stream and depresses intestinal motility in doses which are a small fraction of that required to block the excitatory effects on the intestine produced by vagal stimulation, either a new, i.e., direct, action of atropine must be postulated or it must be concluded that some of the acetylcholine which is being produced continuously in the intestine is exerting a stimulant effect on intestinal tonus. In the latter interpretation is inherent the concept that the acetylcholine either is not produced at the same site as that which mediates excitatory influences seen during vagal stimulation or, more likely, that acetylcholine is produced at the same sites but that some part of it is acting after diffusion to adjacent smooth muscle cells. The effect of acetylcholine acting after diffusion should be blocked as readily as the effect of intravenously injected acetylcholine.

Under the heading of intrinsic reflexes, in addition to peristalsis, contraction of the intestine in response to stretch requires consideration.[80] It is not known, however, whether this is an intrinsic reflex or simply contraction of the muscle coats in response to stretch. This type of response is not observed when the sympathetic nerves to the intestine are intact because the intestino-intestinal inhibitory reflex counteracts the local response. The local contractile response to stretch is seen regularly in the freshly extrinsically denervated small intestine of the dog when the pressure within the lumen is suddenly raised from the normal to, for example, 40 to 80 mm. of mercury by the introduction of fluid into a balloon.[80] When this is done, one sees first the pressure produced passively by the entrance of the liquid into the confined balloon, then a rise in pressure related to a

powerful contraction of the smooth muscle of the bowel wall develops within a second or two and lasts for several seconds. During the contraction the pressure may rise another 40 to 100 mm. of mercury so that in occasional cases a pressure around 200 mm. of mercury may be attained as a result of the active process. Usually, only one peak of pressure is produced following the sudden filling of the denervated intestine and after this there is a slowly progressing decrease in pressure. However, in some cases additional "spikes" of pressure appear, and under some circumstances a sudden spasm of the denervated intestine may occur "spontaneously." When the sympathetic nerve supply of the intestine is intact, distention elicits only the inhibitory response which is a manifestation of the intestino-intestinal inhibitory reflex.

There is evidence that the excitatory response in the ileum which occurs shortly after entrance of food into the stomach (gastro-ileal reflex) is mediated by intrinsic mechanisms.[81–83] The response is not eliminated by bilateral vagotomy and it does not occur in a modified Thiry-Vella type segment of ileum having its extrinsic innervation intact. Its dependence on the continuity of the bowel implicates intrinsic mechanisms. The gastro-ileal reflex does not depend on the entrance of contents into the intestine from the stomach. It is elicited by entrance of contents into the stomach or even by mechanical stimuli in the gastric lumen. It is probably simply the propagation of peristaltic waves from the stomach along the entire length of the small bowel.

Delayed motor responses of the small bowel following feeding have been reported to occur in discontinuous segments of the bowel and evidence has been obtained that this response is dependent on the extrinsic nerves.[84,85] The delayed response is different than the gastro-ileal reflex and it is possible that it is related to influences arising from the small intestine during the period when the intestine is relatively filled following a meal.

EXTRINSIC GASTROINTESTINAL REFLEXES

Motility in a given part of the gastrointestinal tract ordinarily is determined by the local and reflex responses to contents at this site and by reflex influences from other parts of the bowel. Under special circumstances the motility is affected by influences originating on a reflex basis from other organs or by influences from higher centers of the brain.

Duodeno-gastric Reflexes. The motility and the emptying of the stomach are influenced by long reflexes originating from the duodenum.[86–88] Reflex influences on gastric motility elicited by stimuli in the duodenum are known as enterogastric reflexes.[89,90] Duodenogastric, perhaps, would be a better term since reflexes from the jejunum and ileum, which appear to involve somewhat different pathways, also would be included under the heading of enterogastric.

Inhibitory influences upon gastric motility and increased tonus of the pyloric sphincter can be elicited by distention or mechanical stimulation of the duodenum[89,91] or by the introduction of certain substances into the duodenum.[89] Thus there are both mechanically induced and chemically induced duodenogastric reflexes. The pattern of response of the stomach and pyloric sphincter is similar in the two types, and the value of the reflexes appears to be the protection of the duodenum from overdistention or excessive irritation. Evidence has been presented that the duodenogastric reflexes are mediated largely or exclusively through the vagus nerves.[89] They can occur in the absence of any intrinsic connections.

Reflex Effects from the Biliary Tract. Distention of the biliary tract in the experimental animal causes disturbances in gastric motility. Mild distention may cause a decrease in tonus and motility and sudden severe distention may cause pylorospasm, nausea and vomiting.[92] To eliminate this response it is necessary to destroy both the vagal and sympathetic innervation.

According to the studies of Svien and Mann[93] intestinal motility is not readily influenced by pressure in the gallbladder. Changes are observed, however, following prolonged obstruction of the common bile duct.[94] It seems probable that the vomiting caused by distention of the bile ducts would be associated with the characteristic changes in duodenal and upper jejunal motility that usually precede vomiting.[95,96]

Jejuno-gastric Inhibitory Reflex. An inhibitory effect on gastric motility similar to that produced by duodenal distention is produced also by distention of the jejunum.[97–100] In fact, a sufficiently severe sudden distention of any part of the small intestine will cause atonicity and inhibition of motility of the stomach and the entire small intestine. The reflex inhibition of the stomach elicited by jejunal distention is rela-

tively unimpaired after sympathectomy and in the absence of intrinsic connections between the distended segment and the stomach.[98] After vagotomy alone, inhibition of the stomach still may be elicited by distention of a jejunal segment; but in this case the inhibition develops gradually and after a latent period which is long enough so that it is possible that the inhibition is on a humoral rather than reflex basis. The impairment of the intestino-gastric response following vagotomy is to be contrasted with the absence of effect of vagotomy on the intestino-intestinal inhibitory reflex.

Intestino-intestinal Inhibitory Reflex. The name, intestino-intestinal inhibitory reflex, was given by Hermann and Morin[101] to the inhibition of intestinal motility which is produced by sudden distention of the intestine. This reflex was demonstrated originally in acute experiments on anesthetized animals,[101,102] and the nervous pathways have been studied by the use of Thiry and Thiry-Vella fistulas in unanesthetized dogs.[37,103] Distention of any part of the small intestine may result in inhibition of the small bowel within a latent period as short as two to three seconds. The inhibitory influence may become maximal within the time interval between two rhythmic contractions so that amotility may suddenly replace the normal level of rhythmic activity. Sometimes the latent period is longer and the onset of inhibition is less abrupt.

The thoracolumbar system contains both afferent and efferent pathways for the intestino-intestinal inhibitory reflex,[37,104–107] and the central connections are contained in the spinal cord from the seventh thoracic to the second lumbar segments.[108]

The receptors for the intestino-intestinal inhibitory reflex appear to be sensitized by repeated distentions; also, the longer the section of bowel distended the less the pressure required to elicit the intestinal inhibition.[109] It seems probable that intraluminal pressures within the range produced by strong rhythmic contractions are sufficient to cause impulses to be set up in the afferent nerves and possibly summation of these afferent influences may result in a reflex depressant influence upon the strength of the contractions. The intestino-intestinal inhibitory reflex provides a mechanism for quick dispersion of contents when the intestine is rapidly filled at a given point so that a lower pressure will be produced by this amount of filling than would occur in the absence of the reflex. Since the denervated intestine shows a contractile response to sudden filling,[80] one must consider that the local response of the normally innervated intestine to a given degree of filling represents a balance between the local excitatory response and the reflex inhibitory influences. When intestinal distention reaches pathologic levels, the inhibitory effects may be elicited to the extent of counteracting the local excitatory response. It is well known that severe distention of the small bowel contributes to perpetuation of the inhibition. This is probably caused largely by the intestino-intestinal inhibitory reflex and by interference with circulation through the bowel wall. Evidence for the role of reflexes in producing adynamic ileus is obtained by the beneficial effects of spinal anesthesia in individual cases. The importance of distention as a factor in contributing to ileus is indicated by the rapid recovery which may occur in some cases when decompression of the bowel is achieved by mechanical means. In this connection it is noteworthy that the distention of a Thiry fistula by an air-filled balloon will set off a train of events in dogs which terminates in death after about seven to fourteen days.[110] However, if at any time before the terminal stage the distention is removed, the animal quickly begins to recover; or if the fistula is extrinsically denervated, the animal apparently is uninfluenced by the distention.

The intestino-intestinal inhibitory reflex has a role which is analogous in some respects to that of the carotid sinus reflexes which buffer rises in arterial blood pressure. In both cases the reflex is elicited by pressure; the degree to which the reflex is elicited is related to the amount of the rise in pressure and the reflex response is such as to counteract the rise in pressure.

Although the vagi are most important in mediating inhibitory effects to the stomach during duodenal or jejunal distention, there is no evidence that the vagi contain either an afferent or efferent limb for the intestino-intestinal reflex.[10,107]

Reflex Effects from the Anorectal Region. Inhibition of intestinal motility has been observed during defecation in anesthetized dogs;[111] and relatively mild stimuli in the anal canal which elicit contraction of the sphincter in unanesthetized dogs, when the procedure has been repeated sufficiently that alarm is not a factor, cause inhibition of gastric and intestinal

motility.[112] The onset is sufficiently sudden in the case of the intestine to implicate efferent pathways to the bowel. Also, there is evidence for the entrance of adrenergic neurohormones into circulation during rectal stimulation.[113] Inhibition of the stomach and intestine by anorectal stimulation is prevented by abdominal sympathectomy and is uninfluenced by vagotomy, hence the sympathetic system contains the only efferent pathway for the reflex.[113]

The fact that severe inhibition of the stomach and small intestine can be produced by insertion of catheters or instruments into the anal canal perhaps should be taken into consideration in radiologic studies of the gastrointestinal tract when one is looking for changes in motility patterns. Conceivably, a picture of atonicity and amotility of the small bowel could be obtained during a brief period of inhibition produced reflexly by introduction of an enema tip past the anal sphincter.

REFLEX EFFECTS ELICITED FROM OTHER ORGANS

Reflex Effects Elicited by Peritoneal Irritation. The development of adynamic ileus as a complication in patients with peritonitis is a well known occurrence. In the early stages the intestinal inhibition is probably largely on a reflex basis. Mechanical[107] or chemical[114] irritation of the peritoneum causes immediate inhibition of intestinal motility. The reflex inhibitory effects from peritoneal irritation are prevented by procedures which result in the interruption of abdominal sympathetic pathways, namely, splanchnicotomy,[114] spinal anesthesia[115] and splanchnic anesthesia.[116] It appears that the receptors for the peritoneo-intestinal inhibitory reflex are found in both the visceral and parietal peritoneum, and the pathways utilized are predominately in the thoracolumbar system.

According to Walton, Moore and Graham[39] vomiting is produced in cats within six seconds after intraperitoneal injection of 10 cc. of a 50 per cent turpentine emulsion. The shortness of the latent period would indicate a reflex basis rather than an effect produced by the turpentine after absorption into the circulation. As further evidence for the neural basis for vomiting produced by peritoneal irritation, it was demonstrated that the peritonitis caused by E. coli regularly caused vomiting in normal cats and dogs but failed to cause vomiting in animals which had been subjected to vagotomy and abdominal sympathectomy. Both of the denervations were necessary before vomiting was prevented, and the denervated animals were still capable of vomiting in response to emetics.

Reflex Effects from the Urinary Tract. Disturbances of gastrointestinal motility are prominent in patients with diseases of the upper urinary tract.[117] Nausea and vomiting may be the first complaints, and adynamic ileus may be produced by various renal operations and by urolithiasis. In Dietl's crisis there is sudden obstruction of the ureter by kinking, causing a rise in pressure in the renal pelvis, and this elicits nausea and vomiting.

King[111] observed that inhibition of jejunal motility may occur during micturition. Distention of the urinary bladder in dogs causes inhibition of motility; and if the filling of the bladder is rapid and severe, complete amotility of the intestine is induced.[93] Sudden distention of the ureter will produce immediate and complete inhibition of the small intestine and recovery of motility may not occur until several minutes after removal of the ureteral distention.[93] Pinching or pulling on the ureter in unanesthetized animals causes a decrease in intestinal tonus and motility.[118]

Also, marked alteration of gastric motility and vomiting movements have been produced in dogs by pressures in the pelvis of the kidney within the range of the maximal secretory pressures.[119]

Reflex inhibition of the gastrointestinal tract may result from handling the intestine and from severe noxious stimuli in various other structures. In occasional instances the inhibition may be a factor in the development of adynamic ileus.[120] Also, it should be recognized that anything which will cause reflex liberation of epinephrine may cause inhibition of gastrointestinal motility exclusive of influences mediated by the adrenergic innervation to the gastrointestinal tract; thus periods of inhibition of gastric and intestinal motility may be produced by severe arterial hypotension, asphyxia and anoxia.

EFFECTS FROM THE HYPOTHALAMUS AND CEREBRAL CORTEX

The relationship of the parts of the central nervous system to the functioning of the autonomic system have been determined largely by observing changes elicited during stimulation or following ablation of the structures in question. The results of stimulation of the central

nervous system must be interpreted with even greater caution than the results obtained by stimulation of peripheral nerves. Direct stimulation may cause simultaneous activation of centers which normally are not simultaneously activated or which are reciprocally affected. Attention to the latent periods from the time of application of the stimulus until the time of the earliest response may be of use in establishing that a relatively direct pathway to the visceral organ is involved. If the latent period is longer than a circulation time, the possibility of humoral effects or of quite indirect neural effects must be considered. Deficits occurring as a consequence of ablation perhaps are more susceptible to evaluation than the effects of stimulation unless the latter effects occur within a few seconds.

Hypothalamus. Centers concerned with the regulation of visceral functions are contained in the hypothalamus in the ventral portion of the diencephalon. Stimulation or ablation of structures in this region produce changes in gastric and intestinal motility.

The earlier studies on the effects on gastrointestinal motility of stimulation of the hypothalamus and cerebral cortex are reviewed by Miller.[121] More recently Beattie and Sheehan[122] produced excitatory responses in the stomach by stimulating the tuber region in cats, and abolished the response by vagotomy. Inhibitory effects on gastric motility were produced by stimulation of the posterior hypothalamus, and in most cases, the latent periods were short enough to indicate neural effects rather than humoral mediation from other organs. Electrical stimulation of the lateral hypothalamic area was shown by Kabat et al.[123] to produce inhibition of the stomach and intestine whereas currents of similar strength applied to adjacent parts of the brain had no effect. The latent period was as short as one or two seconds. These workers failed to produce increased motility by direct stimulation of the hypothalamus in this study but stimulatory influences were observed in a subsequent study from the same laboratory.[124] Several other laboratories have reported the production of both excitatory and inhibitory influences on gastric or intestinal motility by stimulation of the hypothalamus.[125–127] Which type of effect is obtained depends upon the strength and duration of the stimulus as well as the site. More studies are necessary before one can with confidence designate specific nuclei in the hypothalamus as inhibitory or excitatory with reference to gastrointestinal motility; however, the fact that the hypothalamus contains a neural mechanism for influencing gastrointestinal motility still can be appreciated in the absence of such specific information concerning localization.

It appears that lesions of the hypothalamus, especially of the supraoptic and tuberal nuclei, are more prone to cause serious gastrointestinal disturbances and sometimes the development of ulceration than lesions elsewhere in the central nervous system.[128–130] Martin and Schnedorf[131] failed to produce any ill effects in monkeys and cats by small hypothalamic lesions. According to one study extrinsic denervation of the bowel tended to protect against the development of the gastrointestinal lesions.[132]

Cerebral Cortex. Both excitatory and inhibitory influences on gastrointestinal motility have been observed during stimulation of areas in the frontal lobes.[133–137] In some cases excitation was noted in one part of the bowel while inhibition occurred in another portion. This is not surprising since an excitatory effect in one part of the bowel might elicit reflex inhibition of other portions. Recently, Babkin[136,137] found, in studies on dogs under chloralose and urethane, that stimulation of the orbital surface of the frontal lobes and the anterior end of the cingulate gyrus causes changes in antral motility. He did not obtain effects from the cruciate sulcus. According to several reports removal of portions of the frontal lobes or of the motor areas in some species causes disturbances of gastric and intestinal motility which are not seen following operations on other parts of the cerebral hemispheres.[138,139]

Although the information concerning localization is inadequate, it appears that "centers" for influencing gastrointestinal motility are present in certain portions of the cerebral cortex. The centers in the cortex most likely act upon the hypothalamus which in turn acts upon the vagal and sympathetic outflow. Thus there are mechanisms by means of which influences from the higher centers of the brain may be brought to bear upon gastrointestinal motility. Just what purposes these mechanisms serve are not evident. It seems reasonable to assume that under normal conditions the central mechanisms exhibit little activity; or at least if they are active, a balance exists between the excitatory and inhibitory influences so as to maintain an inter-

mediate level of gastrointestinal tonus and motility. Also, it is conceivable that in certain emotional states one or the other of these central mechanisms may become hyperactive and thus result in abnormal motor functions of the bowel.

Psychic Influences. The fact that changes in gastrointestinal motility accompany strong emotions is well known. The changes in bowel motility may be acute or prolonged, and either inhibition or excitation may be observed. Cannon was most concerned with the inhibition of motility which occurs in those situations which elicit "mass discharge" of the sympatho-adrenal system.[140,141] In these situations the function of the bowel may be depressed or suspended. Momentary inhibition of the motility of the bowel probably contributes to the "gone" feeling in the "pit of the stomach" but does not constitute a clinical problem. It seems unlikely that chronic severe inhibition of the stomach or small bowel can be produced on psychic bases.

More recently attempts have been made to relate changes in gastric motility to the different types of emotions, and gastric hypermotility and hypersecretion accompanying certain emotions have been demonstrated. Wolf and Wolff[142] describe two patterns of response; one consists of hypomotility, hyposecretion and blanching of the mucosa, and the other consists of hypermotility, hypersecretion and reddening of the mucosa. The former pattern is similar to that produced by injection of epinephrine and the latter can be produced by the injection of acetylcholine into the arterial blood supply of the stomach or by intravenous injection of compounds such as carbaminoyl choline (doryl®) or carbaminoyl beta methylcholine (urecholine®). Hence, it appears that postganglionic cholinergic neurons supplying the bowel are selectively activated when a person is under certain types of stress while adrenergic neurons are selectively activated under other types. Resentment and nervous strain produce hyperactivity of the cholinergic nerves to the bowel, at least in some individuals, and it is reasonable to consider that this may predispose to the development of peptic ulcer.

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Clinico-pathologic Conference

Progressive Visual Loss, Right-sided Weakness and Sudden Death

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, G. D. (No. 203760), was a Negro housewife, fifty-two years of age, who was admitted to the Neurosurgical Service of the Barnes Hospital on November 27, 1951, complaining of dimness of vision for four weeks. In 1950 she was admitted to another hospital with symptoms suggestive of acute cholecystitis. Cholecystograms were said to have revealed an abnormal gallbladder. Mild diabetes was also discovered but was easily controlled by diet. The patient had never had visual symptoms or symptoms referable to the nervous system prior to the present illness.

About four weeks before entry the patient was struck on the right side of the forehead with a plastic phonograph record and sustained a superficial laceration with local swelling. One week later she developed right frontal headache, and dimness and blurring of vision in the right eye. Loss of vision was progressive on the right so that by the time of admission the patient was completely blind in that eye. She also complained of mild pain behind the right eye. Four days before admission dimness of vision was noted in the left eye and was likewise progressive. Headache became generalized. There was no history of vomiting, convulsions, personality changes or other neurologic symptoms.

At the time of entry physical examination revealed the temperature to be 37°c., pulse 68, respirations 16 and blood pressure 130/70. The patient was an alert, cooperative middle-aged Negress who was in no distress. Vision was absent on the right and markedly diminished on the left. The right optic disc was hazy and distinctly elevated. Similar changes were present on the left but were less marked. The pupils were dilated and fixed to light and accommodation. In the right fundus one small dark area was seen which was thought by some observers to represent an old hemorrhage. The extra-ocular movements were normal and both corneal reflexes were present. There was slight asymmetry of the face with drooping of the right corner of the mouth; mild drift of the right upper extremity with slight weakness and terminal tremor was noted. There were no other demonstrable abnormalities of the cranial or peripheral nerves. The right lobe of the thyroid was enlarged two times and was firm but not hard. The liver edge could be felt 2 cm. below the right costal margin. The remainder of the physical examination was normal.

The laboratory data were as follows: Blood count: red cells, 5,070,000; hemoglobin, 15 gm.; white cells, 6,200; differential count: 1 basophile, 1 eosinophile, 5 stab forms, 65 segmented forms, 25 lymphocytes, 3 monocytes. Urinalysis: albumin, 1+; sugar, negative; sediment, many white blood cells per high power field. Blood cardiolipin test: negative. Blood chemistry: Non-protein nitrogen, 21 mg. per cent; fasting blood sugar: 90 and 188 mg. per cent on two determinations; total protein, 8.9 gm. per cent; albumin, 4.8 gm. per cent; globulin, 4.1 gm. per cent. Liver function tests: within normal limits. Electrocardiogram: within normal limits. Electroencephalogram: mild fast dysrhythmia indefinite in relation to the complaint. Skull films: negative. Sinus films: clouding of right frontal sinus and of the left ethmoidal air cells. Lumbar puncture: cell count: 160 without acid; 1 with acid; initial pressure, 80 mm. of water; final pressure, 70 mm. of water after removal of 5 cc.; protein, 37 mg. per cent; colloidal gold curve, 0000000000; Wassermann, negative. Radioactive diiodofluorescein was introduced intravenously; there was an increase in over-all radiation but no localization.

Shortly after admission ventriculography was

performed through burr holes in the parietal region. The ventricular system appeared normal. Following the ventriculogram the patient had a severe headache and slight fever but was otherwise well. Because it was believed that the most likely diagnosis was retrobulbar neuritis, she was transferred to the medical service for treatment with cortisone which she was given for ten days in a dose averaging 150 mg. daily. This treatment seemed to result in improvement as evidenced by the fact that the patient had some return of vision in the right eye. Concomitantly, however, there was progressive weakness of the right arm and leg, and during the period of therapy Hoffman's and Babinski's signs became positive on the right. The corrected sedimentation rate was 45 mm. per hour. Lumbar puncture was repeated but the fluid was found to be entirely normal. The patient was afebrile, except for the brief period following ventriculography. Her pupils remained dilated and immobile.

On the thirteenth hospital day the patient suddenly collapsed and could not be aroused. She was seen by a house officer within one or two minutes; he noted that the heart rate was slow and the heart sounds of good quality, but blood pressure was unobtainable. Breathing was sterterous. Shortly thereafter the heart sounds became inaudible, and despite emergency measures the patient died.

CLINICAL DISCUSSION

DR. VIRGIL SCOTT: Our first problem is to determine whether the patient was suffering from one or from two diseases; that is, whether she had a primary neurologic disorder, or whether she had a systemic disease with neurologic manifestations. Among the possibilities to be considered are that the neurologic manifestations arose on the basis of trauma, brain tumor (either primary or metastatic), degenerative disease, or perhaps vascular disease other than that produced by trauma. To review briefly the history, it will be recalled that the patient was a fifty-two year old Negress who had mild diabetes, well controlled by diet alone. She had been well except for symptoms suggestive of gallbladder disease. Four weeks before entry she was struck on the right forehead with a plastic phonograph record and sustained a superficial laceration. One week passed uneventfully, and then she developed right frontal headache, and dimness and blurring of vision in the right eye which was rapidly progressive and which ultimately led to blindness in four weeks. Four days before admission dimness of vision appeared on the left and visual loss was likewise progressive in this eye. Her headache became more severe. There was no vomiting, convulsions, personality change or other neurologic symptoms. Dr. Schwartz, considering all the symptoms which led to the patient's hospitalization, and recalling that she had been struck on the head by a phonograph record, do you believe that trauma may conceivably have been related to her illness?

DR. HENRY G. SCHWARTZ: Yes, I believe that it may have been although it probably wasn't.

DR. SCOTT: If you assume that her difficulty arose on the basis of trauma, what type of pathologic process would you consider?

DR. SCHWARTZ: A hemorrhage localized to the right parasellar region could have caused this clinical picture. A purely traumatic hemorrhage so localized would be rare, and therefore one should consider a pre-existing congenital arterial aneurysm, or even an arteriovenous aneurysm or fistula between the carotid artery and cavernous sinus. The paucity of findings, however, does not enable one to make the diagnosis of aneurysm or fistula.

DR. SCOTT: Another possibility which was considered when the patient entered the hospital was brain tumor. Where would a tumor have to be located to produce as rapidly a developing clinical course as that exhibited by this patient?

DR. SCHWARTZ: It would be almost impossible to ascribe the patient's signs to a single lesion. A tumor in the right parasellar region, with extension upward into the third ventricle, might cause visual field changes and increased intracranial pressure. The weakness of the right upper and lower extremities could be explained, under such circumstances, on the basis of shift of the brain with compression of the left cerebral peduncles.

DR. SCOTT: In almost every case with neurologic manifestations presented in these conferences, the possibility of encephalitis has been raised. In view of the fact that this patient's spinal fluid was normal on two occasions, does encephalitis enter into the differential diagnosis, Dr. Harford?

DR. CARL G. HARFORD: It would be most unlikely that the patient had encephalitis due to a known virus; almost all of the known encepha-

litides are associated with an increased spinal fluid cell count. Further, fever, headache and stiff neck are common physical signs. Since none of these findings was present, I do not believe that encephalitis need be considered.

DR. SCOTT: I believe that one of the important points in this case concerns the status of the optic fundi at the time of admission. There was a difference of opinion on the part of those who saw her, not only as to the type of process present but also as to the duration of the opthalmoscopic changes observed. Dr. Philip Shahan of the Department of Opthalmology saw this patient three times before her entry into the hospital. Information which he has contributed will perhaps be of aid in deciding whether the patient had papillitis or papilledema. Dr. Shahan first saw the patient on November 12th, fifteen days prior to her entry to the hospital. At that time she complained for the first time of blurred vision in the right eye, having awakened that morning with visual difficulty. At the time of her first examination on November 12th vision in the right eye was 20/120 and there was slight swelling of the optic disc. The vision in the left eye was 20/15. One week later Dr. Shahan again saw the patient at which time she reported further visual loss on the right. At that time vision was 20/240 on the right and 20/30 on the left. When the patient was seen by Dr. Shahan for the third time on November 27th, she had no light perception in the right eye and vision in the left was 20/240. She complained of pounding headaches. Dr. Sanders, it is my impression that it may be difficult to differentiate between papillitis and papilledema. Would you comment on this problem?

DR. THEODORE E. SANDERS: At times it may be very difficult to differentiate the two by opthalmoscopic examination. The chief difference is that in papillitis loss of vision is due to a central scotoma. In this case the loss of vision had been too great and too rapid to have been due to papilledema alone, although the slight elevation of the disc was consistent with mild papilledema. The presence of hemorrhages, which were noted on several occasions, could have been due either to papillitis or papilledema. When I saw the patient at the Opthalmologic Conference, I thought that the signs and symptoms were consistent with the diagnosis of retrobulbar neuritis; the fact that she had pain when she moved her eyes was especially typical since pain behind the eye is a common feature.

DR. SCOTT: Would you clarify the term, *optic neuritis?* As I understand it, there may be inflammation of the nerve head, which is called papillitis, or inflammation posterior to the optic nerve head under which circumstances the diagnosis of retrobulbar neuritis is made.

DR. SANDERS: The lesion itself, its etiology and all of the clinical signs except the appearance of the nerve head may be identical in papillitis and in retrobulbar neuritis; the term used is a function of the site of the inflammatory process. If it is near the eyeball itself, change in the optic disc is more obvious than if the inflammatory reaction is more central.

DR. SCOTT: Then it is conceivable that the optic disc may look normal in retrobulbar neuritis?

DR. SANDERS: That is correct. There is an old colloquialism to the effect that in retrobulbar neuritis "the patient sees nothing and the doctor sees nothing."

DR. SCOTT: I gather then that in your opinion the sudden onset, rapid visual loss and the presence of pain suggested the diagnosis of optic neuritis. Had it been possible to map out the central visual field, one would have been able to be more certain.

DR. SANDERS: Yes, that is true.

DR. SCOTT: During her stay here, as noted in the protocol, the patient had a number of investigative studies including x-rays. Dr. Seaman, will you comment on the roentgenologic findings?

DR. WILLIAM SEAMAN: The skull appeared entirely normal, the sella turcica was not enlarged and there was no evidence of intracranial calcification. The chest film revealed that the heart was of normal size; the lung fields were clear. Films of the paranasal sinuses showed some clouding of the right frontal sinus and of the ethmoids, particularly on the left. Detail films of the optic foramina indicated that they were symmetrical bilaterally, without evidence of bony destruction. The ventriculograms demonstrated that the ventricles were not dilated. There was good visualization of the entire ventricular system except for the fourth ventricle which was not well seen. It was our opinion that the ventriculograms were entirely normal.

DR. SCOTT: Returning to the question of brain tumor for a moment, Dr. Schwartz, do the negative air studies rule out that possibility?

DR. SCHWARTZ: We considered them further evidence that no brain tumor was present.

DR. SCOTT: May air studies be negative in the presence of a brain tumor?

DR. SCHWARTZ: Yes, that may occur rarely.

DR. SCOTT: Is there a particular tumor or a particular tumor site in which negative air studies are especially common?

DR. SCHWARTZ: The tumor would have to be extremely small and lie superfically in the gray or white matter.

DR. SCOTT: In the protocol it is stated that when radioactive diiodofluorescein was injected, there was an increase in over-all radiation but no localization. Dr. Goldring, would you comment on this procedure in the diagnosis of brain tumor?

DR. SIDNEY GOLDRING: Intravenous fluoroscein was originally used as an aid in the diagnosis of abdominal tumor. Its use was based on the premise that although both normal and abnormal tissues exhibited an affinity for fluorescein, tumors usually took up more than normal tissues. The procedure was not very effective when the dye was introduced into the abdomen because both edematous and inflammatory tissue took up the dye in the same way that tumor tissue did. Subsequently, the same method was tried in an attempt to diagnosis and to localize brain tumors. Because of the selective blood-brain barrier, fluoroscein, being an acid dye, does not normally pass the barrier; in the presence of tumor, edema or inflammatory reactions there is an increased passage of fluorescein into the brain.

The method was further modified by tagging the dye with radioactive iodine, I^{131}. This modification thus permitted the determination of the uptake of dye in the brain by measurement of radioactivity over the surface of the scalp. Recently we have found that in the presence of meningitis or, in some instances, encephalitis, there is an increase of radioactivity in the spinal fluid.

DR. CARL V. MOORE: In this case there was described an increase in general level of radioactivity without any localization. What is the significance of this finding?

DR. GOLDRING: It is usually indicative, in our experience, of diffuse inflammatory disease of the brain.

DR. MOORE: What are the results in subdural hemorrhage?

DR. GOLDRING: There is no increased uptake of dye in subdural hematoma. If there is associated brain damage as the result of an injury, one may find increased radioactivity.

DR. SCOTT: The electroencephalogram was reported to have shown a mild fast dysrhythmia, "indefinite in relation to the complaint." Of how much value is the electroencephalogram in determining the presence of a brain tumor, Dr. Levy?

DR. IRWIN LEVY: In the hands of an experienced electrocephalographer like Dr. O'Leary, there is a high correlation between EEG findings and the presence of a space-occupying lesion. Perhaps the electroencephalogram is not quite as accurate as a ventriculogram, but I think that in 80 to 85 per cent of cases it is of significant help. This patient's record constituted evidence against either tumor or generalized increase in intracranial pressure.

DR. SCOTT: For the many reasons mentioned it seems clear that brain tumor may be eliminated from further consideration. Returning then, Dr. Sanders, to your suggestion of optic neuritis, does the fact that the x-rays of the sinuses revealed some clouding have significance in regard to that diagnosis?

DR. SANDERS: Years ago it was common practice for patients to be subjected to sinus drainage whenever the diagnosis of optic neuritis was entertained. It is now believed that sinus drainage is of no value in the treatment of optic neuritis and the procedure is no longer generally used. It is true, of course, that the posterior ethmoid sinuses and the optic nerves lie close to one another, and in the presence of significant ethmoid sinusitis, the inflammatory reaction conceivably might affect the sheaths of the optic nerve. The normal spinal fluid studies, however, ruled out that possibility in this instance, and I would therefore disregard the clouding of the sinuses demonstrated by x-ray.

DR. SCOTT: This patient received cortisone. What has been the experience in the use of cortisone in the treatment of optic neuritis?

DR. SANDERS: It should be pointed out that most cases of optic neuritis are not as marked as this one nor as rapidly progressive; many of them are unilateral and frequently the patients recover spontaneously. For these reasons, and because cortisone has not been used long enough, its value in optic neuritis cannot as yet be assayed.

DR. SCOTT: Dr. Levy, do you have any suggestions as to the cause of this patient's symptoms?

DR. LEVY: Acute multiple sclerosis and neuromyelitis optica should be considered; whether these are the same or different diseases is a debated point. It should be noted that this woman, at the age of fifty-two, was in an age group older than are most patients when they suffer their first episode of multiple sclerosis. Rarely, arteriosclerotic changes may give rise to symptoms similar to those recorded here. Finally encephalopathy arising on the basis of one of the diseases of hypersensitiveness, e.g., polyarteritis nodosa, may be mentioned.

DR. SCOTT: During the period that this patient was receiving cortisone, she developed progressive weakness of the entire right side of her body. Is that compatible with neuromyelitis optica?

DR. LEVY: Yes, it is. There may be a difference in time of onset between the optic nerve changes and those in the rest of the central nervous system.

DR. SCOTT: Dr. Sanders, in your opinion what was the nature of this patient's disease process?

DR. SANDERS: It was our belief that the patient had neuromyelitis optica. Most patients with this syndrome also have the signs of transverse myelitis, usually at a low level. This patient, on the other hand, had a relatively high, unilateral lesion.

DR. SCOTT: Are there other comments?

STUDENT: The patient had fixed dilated pupils before she became blind. Is that finding compatible with optic neuritis?

DR. SANDERS: That is a very good point. Fixed dilated pupils occur in optic neuritis only after there has been complete loss of vision. In this instance we would have to assume that some other neurologic lesion accounted for the fixed pupils which, as you point out, were present before vision was lost. It should also be mentioned that patients with neuromyelitis optica do well; it is rare for them to succumb to the disease.

DR. SCOTT: We shall now turn to consideration of the cause of death. The patient was apparently quite well on the last hospital day when she suddenly collapsed and died shortly thereafter. We usually consider coronary occlusion and pulmonary embolism as the common causes of sudden death. Dr. Rosenbaum, in this patient should an intracranial lesion be considered?

DR. HERBERT E. ROSENBAUM: Massive hemorrhage can produce sudden death; vascular accidents involving the spinal centers particularly may lead to rather rapid exitus. I would be more inclined, however, to believe that death in this case was the result of a lesion outside of the central nervous system. Pulmonary embolism would be compatible with the description of the terminal episode.

DR. SCOTT: This patient had developed paralysis on one side some days prior to death. In reference to the possibility of pulmonary embolism, is there any evidence to support the postulate that patients who are paralyzed are prone to develop phlebothrombosis of affected extremities?

DR. ROSENBAUM: Yes, I think that is true.

DR. SCOTT: In summary, it seems that the diagnosis of neuromyelitis optica would fit the clinical picture exhibited by this patient. Acute multiple sclerosis, according to some authorities the same entity as neuromyelitis optica, must also be considered seriously. The terminal event was probably a pulmonary embolus.

Clinical Diagnoses: Neuromyelitis optica or acute multiple sclerosis; pulmonary embolism.

PATHOLOGIC DISCUSSION

DR. MICHAEL MCNALLEY: The external appearance and abdominal viscera revealed no relevant lesions. A number of large laminated thrombi with distinct valvular markings were found in the right ventricle and filled the main and secondary pulmonary arteries. Although no additional thrombi could be expressed from the veins of the legs, no other source of these emboli was found. The external appearance of the brain was normal except for small hemorrhagic discolorations in the parietal cortex beneath the trepanned holes. In the posterior limb of the left internal capsule there was an area, measuring 1½ by 1½ by ½ cm., of gelatinous pinkish and obviously demyelinated tissue. Above the lesion there were several semi-translucent areas 5 or 6 mm. in length that radiated upward into the white matter. On the right a similar area 1 by 1½ cm. in size lay immediately adjacent to and above the lentiform nucleus and contained a small central cavity filled with blood. This lesion extended to the posterior extremity of the tail of the caudate nucleus and then upward to be continuous with the laceration in the cortex beneath the burr hole in the skull. A lesion similar to those in the internal capsules was present subcortically on the lateral surface of the left occipital lobe. This lesion was entirely

independent of any needle tract. No other plaques were grossly detectable in step sections of the remainder of the brain and spinal cord. The gallbladder was thickened and contained a large solitary stone.

DR. DAVID E. SMITH: It should be emphasized that although the two largest of these foci of demyelination were apparently crossed by the needle tracts of the ventricular punctures, they did not have the usual appearance of such tracts. They extended further superiorly and laterally than the needle tracts and had very little hemorrhage to suggest a traumatic orgin. The third and smaller lesion beneath the occipital cortex was of the same gross appearance and unquestionably was unassociated with a needle tract. The optic nerves and right eye were examined; I would like to have Dr. Sanders discuss the preparations.

DR. SANDERS: The section in Figure 1 I take to be representative of mild papilledema. There is no cellular reaction in the nerve head and very little elevation. The nerve fiber layers in the retina are continuous with the nerve fibers in the optic nerve. When edema involves the optic nerve head it usually extends out into the retina, and swelling occurs laterally as well as vertically. One of the best histologic indications of papilledema is therefore a pushing aside of the rod and cone layers of the retina about the disc. On the right side of this figure the rod and cone layers come up normally almost to the edge of the optic nerve while on the left they are displaced laterally. This is how papilledema produces enlargement of the blind spot. In sections of the optic nerve itself (Fig. 2) there is not much cellular infiltration, but there is a general loss of the orderly architecture of the columns of the optic nerve. This finding suggests a breakdown of the optic nerve itself, and stains for myelin showed a definite diffuse loss of that substance. There was present, therefore, definite although relatively mild optic neuritis. I would like to ask if the large demyelinated plaques in the posterior parts of the internal capsules involved the optic radiations? The clinical picture did not suggest a primary lesion of the optic tracts.

DR. SMITH: The plaques were sufficiently high in the white matter that they did not involve enough of the optic radiation to allow us to predict that any of the clinical symptoms were on that basis.

Figure 3 is a low magnification of a myelin preparation of the single plaque from the occipital cortex. This focus lies largely in the white matter in an immediately subcortical position. It is rather sharply outlined and is characterized by a complete loss of myelin. The histologic appearances of all three plaques are identical. They are filled almost entirely by large mononuclear cells separated by coarse segments of persistent nerve and glial fibers as is shown in Figure 4. Figure 5 is a view of the center of one of the large plaques and shows the greatest vascular reaction that was found—a slight and non-specific infiltration of lymphocytes about the vessels. There are no thrombi in these vessels. Nearly all the cells in these plaques are filled with fat vacuoles. In other words, they are macrophages or, if you will, activated microglia or compound granular corpuscles. The uniform presence of this particular cell type suggests that these are areas of relatively recent destruction of myelin in which the stage of phagocytosis and mobilization of the broken lipid compounds is still dominant. Figure 6 shows that there is persistence of a large number of the axons running through these demyelinated plaques. Actually, the frequent and irregular bulbous swellings along these structures suggests they are also damaged although not destroyed.

Therefore, this process represents a disease of the central nervous system manifested by papilledema, demyelination of the optic nerve and three demyelinated plaques, two of which are of considerable size and in the posterior limb of each internal capsule and one beneath the occipital cortex. The brain stem and spinal cord were carefully examined without finding other plaques, but these three plaques show a characteristic reaction of acute destruction of myelin and intense infiltration of macrophages with preservation of the neurons and no evidence of primary vascular involvement. These are the essential characteristics of an acute lesion of multiple sclerosis. The scanty distribution of the plaques is disappointing, but it must be remembered that this patient died as a result of an accident which was not part of the primary disease. The acute nature of these plaques and their small number are obviously compatible with the scarcity of symptoms. Those symptoms and signs relative to the eye are explained by the extent of the changes

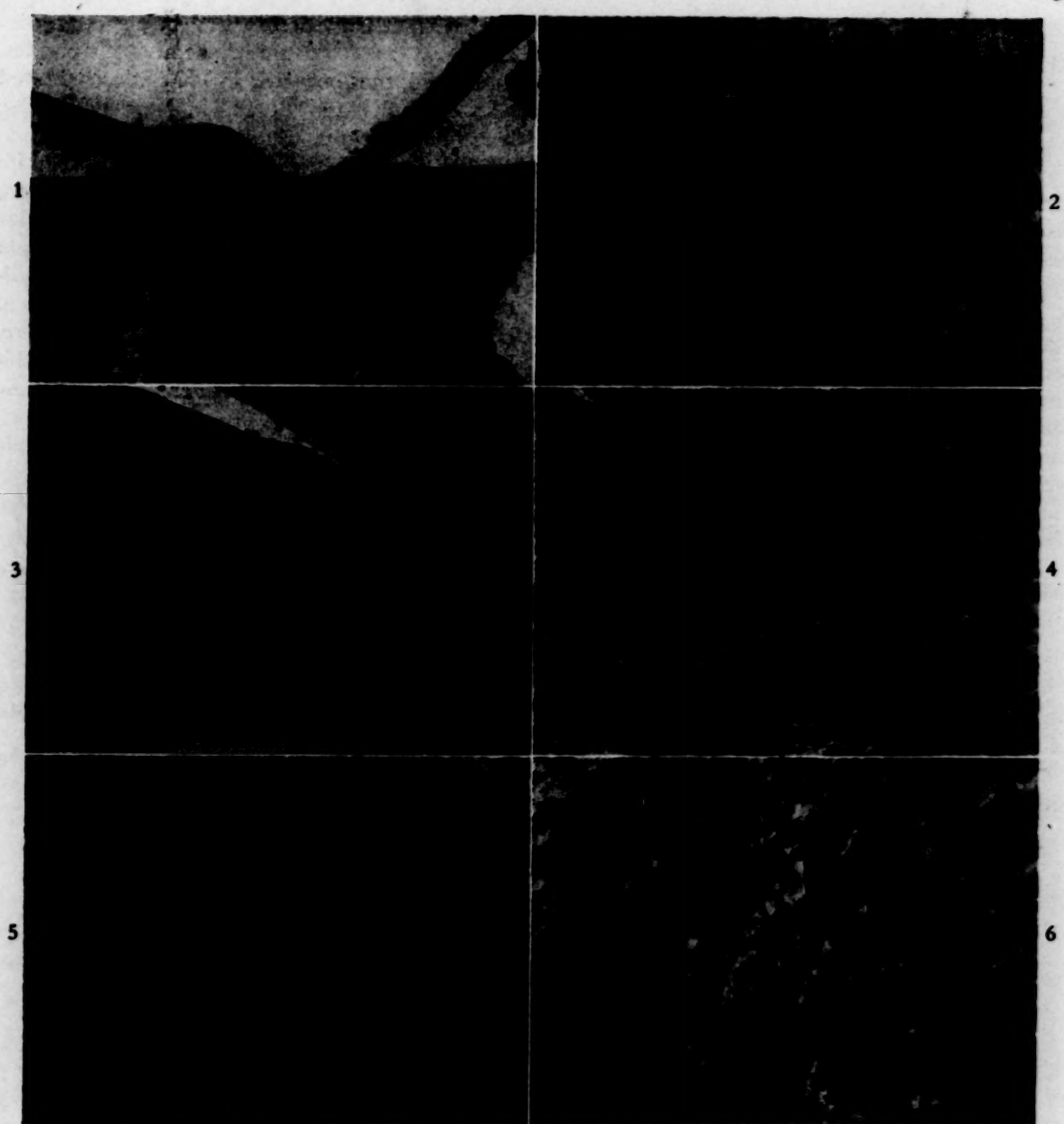

FIG. 1. The optic disc and nerve head: the lateral swelling and displacement of the rod and cone layer due to papilledema is present on the left while the right side of the disc shows a more normal relation to the retina.

FIG. 2. Disorderly arrangement and loss of the columnar arrangement in the cells of the retro-orbital optic nerve in mild optic neuritis. Diffuse demyelination in this region was also demonstrated.

FIG. 3. The isolated plaque of demyelination beneath the occipital cortex.

FIG. 4. The large fat-filled macrophages that were uniformly present throughout all three plaques.

FIG. 5. Slight perivascular lymphocytic infiltration in the center of a large plaque; this was the greatest involvement of vessels that was found.

FIG. 6. Persistent but swollen axon cylinders in a plaque; Bielschowsky silver preparation.

demonstrated in the retrobulbar nerve in the eye that was examined histologically.

There are several things that might be said about the atypical qualities of this case. In the first place, this is a rather old patient to have a first episode of multiple sclerosis. However, in various series between 10 and 15 per cent of cases of multiple sclerosis begin after the age of forty years. The occurrence of the disease in a Negro is also considerably less common than in members of the white race in the United States. The large plaques are in typical paraventricular positions, but to explain the small number of lesions this must be considered a very early case. The absence of changes in the spinal cord has prevented the recognition of this as the syndrome of neuromyelitis optica, but the lesions in the eye and brain are qualitatively identical in that disease and in multiple sclerosis.

The pulmonary embolus that was the terminal episode in this case apparently developed without the presence of any of the pathologic conditions that usually lead to venous thrombosis. This woman was not on complete bed rest, she had no cardiac disease and she had no evidence of local thrombophlebitis or phlebothrombosis. The therapy with cortisone for ten days before she died, however, is highly reminiscent of the reports of Cosgriff and others[1,2] who recognized as many as forty thromboembolic episodes, some fatal, that occurred in 700 patients treated with cortisone and ACTH in New York. The length of therapy, the dosages of cortisone or ACTH and the age of the patients are quite comparable in those cases and this one; there was no evidence of dominance of any particular primary disease in the series. The phenomenon is not well understood. No chemical or physiologic explanation is obvious; but the clinical coincidence of its occurrence is impressive, especially when it appears in a case such as this one in which there is no other apparent cause of thrombus formation.

Final Anatomic Diagnoses: Acute multiple sclerosis; demyelination of the optic nerve; embolic thrombi in the right ventricle, main and secondary pulmonary arteries.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

[1] Cosgriff, S. W., Diefenbach, A. F. and Vogt, W., Jr. Hypercoagulability of the blood associated with ACTH and cortisone therapy. *Am. J. Med.*, 9: 752–756, 1950.

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Case Reports

Infectious Mononucleosis*

Report of Case with First Appearance of Significant Numbers of Heterophil Antibodies and Abnormal Lymphocytes ("Virocytes") in Seventh Week of Illness

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THE protean nature of the clinical picture of infectious mononucleosis[1–5] has necessarily compelled increased reliance, for purposes of diagnosis, upon laboratory tests. These tests include the finding of abnormal lymphocytes in the peripheral blood[6–10] and an elevation of sheep cell agglutinins in the serum with a characteristic absorption pattern.[11–26] To these diagnostic supports may now be added the finding of hepatic involvement clinically, chemically and histologically.[27–59b]

The characteristic peripheral blood picture is one of early leukopenia followed with relative or absolute lymphocytosis with great numbers of abnormal lymphocytes. These abnormal lymphocytes usually are first observed early in the illness.[1,38,60–68] In our experience with a group of twenty-five sporadic cases the abnormal lymphocytes were first detected, on the average, 9.8 days after the onset of illness, with a spread from one to twenty-one days.[43] This agrees with the reported experience of others. Similarly, significant sheep cell agglutination titers are usually attained within the first two or three weeks of illness[1,12,19,38,61,66–69] but exceptional instances have been noted in which these agglutinins have not been detected until the second and third months after the onset of illness.[19,42,58,67,70,71,80,81]

The case herewith reported represents an unusual example of one in which the diagnosis of infectious mononucleosis, although suspected from the onset, could not be made until the seventh week after the onset of illness when for the first time both serologic and hematologic tests became "positive."

CASE REPORT

J. R. W., a twenty-one year old white female college student, became ill on June 8, 1950, with complaints of fatigue, anorexia, mild upper abdominal discomfort and fever which reached 104°F. within the first twenty-four hours. Her past history included the usual childhood infectious and contagious diseases, numerous food allergies with digestive manifestations and persistent eosinophilia for which no adequate etiology could be found. The eosinophil count had been as high as 40 per cent on some occasions.

Physical examination at onset of the illness revealed, in addition to the high fever, slight anterior and posterior cervical lymphadenopathy bilaterally and a tender, palpable liver edge just below the right costal margin. No other physical abnormalities were noted at that time. In the course of the next four days the lymphadenopathy extended to include the axillary, inguinal and femoral nodes bilaterally, with progressive increase in the size of the individual nodes. Hepatomegaly also increased until the liver was palpable 4 cm. below the right costal margin. The spleen could not be felt. No rash was noted.

The initial blood count on June 9th showed 6,800 leukocytes per cu. mm., of which 46 per cent were lymphocytes, 3 per cent monocytes, 38 per cent neutrophils, 11 per cent eosionophils and 2 per cent basophils. Two abnormal lymphocytes of the type found in virus infections[78] were seen. The sheep cell agglutination titer on June 12th was 1:28. The serum bilirubin was 0.40 mg. per cent; the thymol turbidity test was

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TABLE I

LABORATORY DATA IN CASE REPORTED

Date	Total (per cu. mm)	White Blood Cell Counts — Per cent						Sheep Cell Agglutination Titers			Blood Chemical Examinations					
		Neutrophils	Eosinophils	Basophils	Monocytes	Lymphocytes	Abnormal Lymphocytes	Unabsorbed	after Absorption with		Bilirubin Total (mg. %)	Thymol Turbidity (Units)	Cephalin Flocculation (at 48 hr.)	Alkaline Phosphatase (Bodansky Units)	Cholesterol (mg. %)	
									Guinea Pig Kidney	Beef Cells					Total	Esters
1950																
June 9	6,800	38	11	2	3	46	(2)									
12	7,750	41	14		5	40	(1)	1:28			0.4	1.73†	3+		95	55
19								1:56				3.95†	1+		198	143
26								1:56				1.73†	0			
July 10	15,000	66	14		2	18		1:56	1:3.5	1:7	0.4	1.78†	2+			
17	12,500	15	1		2	82	(30)	1:112			0.8	2.90†	2+		168	113
22	14,600	17	1			82	(several)									
23		23	4	1		72	(many)									
24								1:1792			0.3	10	28+‡	10.9		
Aug. 3								1:3584			0.4	8	13+‡	4.1		
4	9,200															
11											0.2	6	14+‡	3.6		
14	14,250	24	23		3	50	(4)									
17								*1:224	1:112	1:<7						
Dec. 19								*1:56	1:<7	1:<7	0.95	2.5	1+			
1951																
Apr. 10	14,400	41	27		1	31	(2)	1:28			0.4	2.5	0			

* These heterophil antibody determinations, with absorptions, were performed by laboratory of Dr. Annis E. Thomson, New York City Department of Health.

† These thymol turbidity determinations were made by the method of Ley, Lewis and Davidson (*J. Lab. & Clin. Med.*, 31: 910, 1946) expressed in cubic centimeters of barium sulfate suspension with normal values up to 1.68; in all other thymol turbidity determinations the method employed was that of MacLagen (*Brit. J. Exper. Path.*, 25: 234, 1944) as modified by Shank and Hoagland (*J. Biol. Chem.*, 162: 133, 1946) with normal values up to 4.0 units.

‡ These cephalin-cholesterol flocculation determinations were made by a modification of the Hanger technic as described by Frisch and Quilligan (*Am. J. M. Sc.*, 212: 143, 1946). In this method the total number of plusses in 7 serial dilution tubes are recorded after incubation at 5°c. for a period of 18 to 20 hr. Normal values are up to 10+. In all other cephalin-cholesterol flocculation tests recorded in the table the technic of Hanger (*Tr. A. Am. Physicians*, 53: 148, 1938) was employed. Normal values were up to 2+ at 48 hr.

at the upper limit of normal, 1.73 cc. (by method of Ley, Lewis and Davidson,[7] Table 1); the cephalin flocculation test was 3 plus in forty-eight hours; the total cholesterol was 95 mg. per cent; and the free cholesterol was 40 mg. per cent, a decrease in both the total cholesterol and the esters. The aforementioned and subsequent laboratory findings are shown in Table 1.

After the first week the temperature subsided to normal levels, the lymph nodes decreased in size but did not disappear entirely and the liver was no longer palpable. There was, however, some residual tenderness in the right upper abdominal quadrant. At the end of the third week of the illness very limited activity was permitted but this was followed within a few days with the onset of diarrhea. There was no recurrence of fever, no increase in the lymphadenopathy and no recurrence of hepatomegaly. The diarrhea ceased spontaneously after one week but the next day, July 10th, the temperature rose to 101°F. and was accompanied with an increase in the size of the cervical lymph nodes, with a particularly large node appearing at the angle of the left mandible. On this date, the thirty-third day since the illness began, the peripheral blood picture still did not suggest a definite diagnosis and the sheep cell agglutination titer (1:56), although one dilution higher than originally, revealed normal Forsmann antibodies on absorption with guinea pig kidney and beef cells. For the ensuing week the temperature ranged from 98° to 101°F., with listlessness and general malaise as the only subjective complaints.

Physical examination on July 17th (fortieth day after onset) revealed moderate pallor, enlargement of the cervical lymph nodes including one the size of a large hazel nut at the angle of the left mandible, enlargement of the left axillary lymph nodes and recurrence of hepatomegaly to 4 cm. below the right costal margin. The individual lymph nodes were firm, discrete, slightly tender and not fixed to the surrounding tissues. A blood count revealed 12,500 leukocytes per cu. mm., of which 82 per cent were lymphocytes and 30 per cent of these lymphocytes were abnormal. A heterophil antibody test on the same date was positive in a dilution of 1:112. No absorption tests were done on this serum specimen.

On July 19th the lymph nodes were slightly larger and for the first time in the illness the edge of the spleen was palpable below the left costal margin. In addition, a small purpuric lesion had appeared at the medial aspect of the left elbow. That evening the patient had a severe chill and her temperature rose to 105°F.

On July 22nd, the forty-fifth day following onset of her illness, the patient was admitted to the Infectious Disease Service of the New York Hospital where her course was one of steady improvement. Her temperature reached 101°F. daily for the first three days, ranged between 100° and 100.4°F. for the next week and thereafter remained within normal limits. Heterophil antibody titer rose to 1:1792 on July 24th and reached a maximum of 1:3584 on August 3rd (fifty-seventh day of illness). The patient was asymptomatic except for easy fatigability and was ambulated at the end of the third week. She was discharged improved on August 12th. The final diagnosis was infectious mononucleosis with anicteric hepatitis.

The patient has remained well since her discharge from the hospital and there have been no recurrences of the disease. Follow-up laboratory data are indicated in Table 1. It will be noted from this Table that on August 17th (seventy-first day after the illness began) the heterophil antibody titer was still elevated (1:224) and absorption tests were typical of infectious mononucleosis. When this test was next repeated four months later, the titer had fallen to 1:56 and the results of the absorptions indicated that the antibodies were now of the Forsmann type rather than those seen in infectious mononucleosis. When this examination was last performed ten months after the onset of the original illness, the titer was 1:28, the same as at the onset.

COMMENTS

The experience with this case underscores the difficulties in differential diagnosis of infectious mononucleosis. This is particularly significant when a diagnosis with much more serious import, such as Hodgkin's disease, demands consideration. The distinction between infectious hepatitis and infectious mononucleosis, while often difficult, is not nearly so urgent because the therapy for both illnesses is along similar lines and the immediate and ultimate prognosis of the two is not so widely divergent.

The late appearance of significant sheep cell agglutinins, even when studies have been made at frequent intervals during the early days of the illness, as in our case, has been previously

pointed out.[19,42,67,70,80,81] Although this is relatively uncommon, it is of sufficient frequency to demand a search for heterophil agglutinins at least into the third month after the onset of illness in any case suspected of infectious mononucleosis before the diagnosis may be discarded. If the patient under study has completely recovered in the interim, it may appear academic to pursue these repeated agglutination tests; but if, as in our patient, symptoms and signs recur, such studies are necessary in order to eliminate the possibility of other more serious illness, such as Hodgkin's disease, leukemia or tuberculosis.

A second point concerns the definition of significant heterophil agglutination titers. To determine this it is first necessary to apply the particular method to normal persons. This has been done with the technic we employ which is essentially that described by Davidsohn.[72] Our results indicate that the maximum titer attained in a group of 200 normal adults is 1:56.[78] However, the level of the antibody titer alone is an insufficient basis for interpreting this test for two reasons: (1) Early in the course of infectious mononucleosis the titers may be low. Moreover, in some cases of infectious mononucleosis no high titer ever appears. Nevertheless, despite these low titers, the antibodies may be detected as infectious mononucleosis antibodies by means of absorption with guinea pig kidney and beef erythrocytes. (2) Occasional elevations in titer occur in diseases other than infectious mononucleosis.[18,73–77]

For these two reasons differential absorption tests are necessary. By their use it is possible in most cases to distinguish the antibodies in infectious mononucleosis from the occasional apparently non-specific (Forsmann) antibody rises in infectious hepatitis, Hodgkin's disease and leukemia.[18,73,75,77] It is our experience[43,73] that a titer of 1:896 hardly requires corroboration of the diagnosis of infectious mononucleosis with absorption tests (although it is always desirable and particularly so in view of a recent report[77] of "normal" antibody rises to 1:896 in two cases of monocytic leukemia); that any titer below 1:896 requires absorption tests for differentiation; that even apparently low levels of titers (1:28, 1:56, 1:112) may occur in infectious mononucleosis with positive (that is, infectious mononucleosis) absorption patterns. Therefore, we define a *significant* titer as one which yields a positive absorption pattern (none or incomplete absorption with guinea pig kidney, complete or almost complete absorption with beef cells) or, for practical purposes when absorption tests are not feasible, a titer of 1:896 or above.

We therefore consider that a titer of diagnostic significance was not attained in our case until the forty-seventh day of illness when the titer was 1:1792. (Table I.) It is unfortunate that no differential absorption tests were performed on the serum specimen of the fortieth day when the unabsorbed titer was 1:112. It is entirely possible that these antibodies were then identifiable by this means as infectious mononucleosis antibodies, which they definitely were not on the thirty-third day. However, even without this differentiation by absorption tests it is fair to assume that at most no more than one week was lost in establishing the positive diagnosis.

The first appearance of abnormal lymphocytes (which we term "virocytes"[78]) in our case was probably early in the first week of illness. However, at this time they were in such sparse numbers and the percentage of total lymphocytes was so little increased above normal that it was difficult to place any specific diagnostic weight upon the finding. This is particularly understandable in light of the occurrence of such findings, in such small degree, in numerous other virus diseases.[78] The emergence of undoubted lymphocytosis of 82 per cent with 30 per cent abnormal lymphocytes on the fortieth day of illness was the first observation of the hematologic picture characteristically seen in infectious mononucleosis. Two points should be made in this regard. First, as we have elsewhere pointed out, although these abnormal lymphocytes are found in a number of virus diseases, only in infectious mononucleosis do they appear in numbers much above 10 per cent and tend to persist for many months.[78] There are rare exceptions in regard to persistence of these cells, as we have observed a case of serum-transmitted virus hepatitis in which the cells were still seen in the peripheral blood twenty-seven months after onset of illness.[79] The second point is that it is rare indeed in infectious mononucleosis for these "virocytes" to make their initial appearance in significant numbers so late in the illness. Recently Sharp[58] reported a case, which came to autopsy examination, in which despite numerous blood examinations the abnormal cells were first observed on the thirty-sixth day of illness. In this case an elevated antibody titer

(1:512) also was first detected on the thirty-sixth day of illness but it appears that no previous heterophil agglutination tests had been performed. Rapaport[38] mentions one case in which the first typical smear of the peripheral blood was discovered on the forty-third day of illness and indicates that previous examinations probably had been performed; also, he stresses the importance of repeated white blood cell counts by pointing to three patients in whom the smear did not become typical until the fourth, fifth and seventh count, respectively (but here the durations of illness are not recorded). However, these instances of late appearance of abnormal lymphocytes in the peripheral blood in cases of infectious mononucleosis are the exceptions to the rule. Generally, the cells are first seen and reach their maximum percentages during the first few weeks of illness.[1,38,43,60–68]

SUMMARY

1. A case is presented of a twenty-one year old female with infectious mononucleosis in whom the diagnosis could not be established until the seventh week of her illness when diagnostically significant numbers of abnormal lymphocytes and heterophil antibodies were first detected in the peripheral blood.

2. This delayed appearance of significant numbers of abnormal lymphocytes and heterophil antibodies is unusual in infectious mononucleosis.

3. The case serves to emphasize that in diagnostic problems in which infectious mononucleosis enters into the differential diagnosis it is important to persist with these hematologic and serologic examinations at least into the third month of illness.

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Effects of Unilateral Renal Vein Hypertension Secondary to Splenorenal Vein Anastomosis on Individual Kidney Function*

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BECAUSE the kidney plays a major role in the body economy of salt and water, this organ has been charged with the ultimate responsibility for retention of these substances during congestive heart failure. The manner in which the failing heart influences the kidney in this regard is a subject under active investigation. It has been suggested by Warren and Stead,[1] Merrill,[2] Mokatoff, Ross and Leiter[3] and others that the decreased excretion of sodium and water in congestive heart failure is primarily related to depressed glomerular activity resulting from reduced cardiac output. On the other hand, Futcher and Schroeder,[4] Borst,[5] Sinclair-Smith, Kattus, Genest and Newman[6] and others suggest a primary increase in renal tubular reabsorption of filtered sodium. Recently, the influence of increased renal venous pressure upon salt and water excretion and glomerular activity has been studied. Blake, Wegria, Keating and Ward[7] have shown that elevation of left renal venous pressure up to 350 mm. of saline solution in the anesthetized dog results in a significant increase of sodium and water reabsorption in the homolateral kidney without altering renal hemodynamics. Selkurt, Hall and Spencer[8] in similarly executed experiments found significant depressions of glomerular filtration at similar levels of renal venous pressure. These latter authors state, however, that the degree of depression of glomerular activity was not sufficient to account for significant sodium retention. Farber, Alexander and Eichna[9] have demonstrated that increasing inferior vena caval pressure in man by means of an inflated balloon attached to a venous catheter results in significant reduction of renal water and electrolyte excretion. This phenomenon occurred whether the venous congestion included the renal circulation or not, and the degree of sodium and water retention could in no way be correlated with renal hemodynamic effects.

Application of the aforementioned experimental data to the situation in chronic congestive heart failure in man is subject to criticism on an essential point. All of the cited experiments have been acute, with observations necessarily limited to relatively short time intervals after experimental elevation of venous pressure. Important physiologic readjustments are known to occur following chronic alterations of the internal environment, as in congestive heart failure. Hence, transposition of data obtained following an acute rise in venous pressure to situations in which there is a chronic elevation of venous pressure calls for cautious interpretation.

The effects of chronic elevation of renal vein pressure upon renal excretion of salt and water in the unanesthetized dog have been studied by Fishman et al.,[10] using experimental pericarditis with effusion; by Hwang et al.,[11] using partial ligation of the inferior vena cava just cephalad to the renal veins; and by Stamler et al.,[12] using partial ligation of the inferior vena cava above the hepatic veins. Although these procedures all resulted in significant and equivalent elevations of renal vein pressure and a similar range of glomerular filtration rates, partial inferior vena caval obstruction just above the renal veins did not result in significant depressions of water and salt excretion, whereas partial obstruction above the hepatic veins and pericarditis with effusion did. These studies suggest that chronic elevation of venous pressure results in salt and water retention through a

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TABLE I

SEPARATE RENAL STUDIES NINE MONTHS FOLLOWING A LEFT SPLENORENAL ANASTOMOSIS FOR PORTAL HYPERTENSION

Period	Renal Clearances						Urine Flow			Electrolyte Excretion												Inulin U/P Ratios		
	C_{IN}			C_{PAH}						Sodium			Chloride			Potassium							
	Right kidney	Left kidney	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L	R	L	R/L
	ml./min.	ml./min.		ml./min.	ml./min.		ml./min.	ml./min.		mEq./min.	mEq./min.		mEq./min.	mEq./min.		mEq./min.	mEq./min.				
Control	46.6	34.5	1.35	156	140	1.12	1.22	0.88	1.39	113	98.9	1.14	93.2	77.8	1.20	19.3	20.7	0.93	41.3	41.6	0.99
Salt Load 1	61.6	36.7	1.68	218	126	1.73	3.00	1.58	1.90	479	261	1.84	471	243	1.94	45.0	47.5	1.06	20.6	23.3	0.88
Salt Load 2	46.6	38.2	1.22	139	141	0.99	2.60	1.85	1.41	476	351	1.36	471	343	1.38	45.5	46 3	0.98	17.9	20.6	0.87

The control values represent the averages of three clearance periods.
The salt-loading periods were fifteen minutes long. The clearance values given are not corrected for surface area.

renal tubular mechanism in some way stimulated by increased hepatic vein pressure. However, data concerning salt and water metabolism gleaned from dog experiments do not necessarily apply to humans, as these two species are known to differ in the manner in which salt and water are distributed and excreted.

Human subjects who have had a splenorenal shunt operation for portal hypertension present almost ideal conditions for study of the chronic effects of increased renal venous pressure. Thus the left renal vein is subject to the increased pressure present in the portal circulation while the right renal venous pressure is normal. The right kidney acts as a perfect control for the left kidney since they are both subject to identical humoral and neural stimuli. Individual kidney clearance studies can be performed using ureteral catheters. Any suitable postoperative period may be allowed to elapse so that the chronic elevation of renal venous pressure of congestive heart failure may be simulated. Such a study was performed in one subject with a splenorenal shunt. The present data representing the results of a single experiment in this one subject are recorded in the hope that they may serve as a stimulus to others who have subjects with splenorenal anastomoses under their surveillance.

CASE REPORT

The subject was a fifty year old woman with proven Laennec's cirrhosis. A splenorenal anastomosis was performed because of severe repeated hematemeses from esophageal varices. The spleen was removed and the splenic vein anastomosed to the renal vein, end to side, about 2.0 cm. from the hilum of the left kidney and 10.0 cm. from the vena caval end of the renal vein. The left kidney remained *in situ*, its capsule undisturbed. The anastomotic channel measured 1.8 cm. in diameter. Before anastomosis the pressure in a branch of the right gastroepiploic vein was 380 mm. of saline solution. Following anastomosis the pressure dropped to 255 mm. Except for the development of an evanescent left pleural effusion the postoperative course was uneventful. The patient has remained free of hematemesis up to the time of this writing, sixteen months from the day of operation.

Nine months following the anastomosis separate renal clearance studies were performed. Number 8 French ureteral catheters were passed up both ureters for a distance of about 10 cm.

in accordance with the technic of Chasis and Redish.[13] Priming and sustaining infusions of sodium, p-aminohippurate and inulin were given intravenously in doses calculated to maintain plasma concentrations of 2 and 30 mg. per 100 ml., respectively. The sustaining infusion,

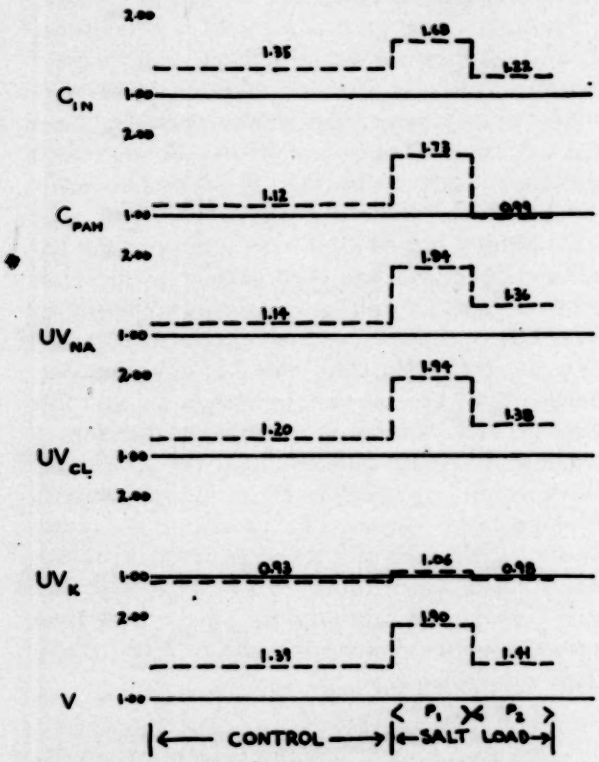

FIG. 1. The ratio of the functions of separate kidneys, right/left, nine months following a left splenorenal anastomosis for portal hypertension. V = urine flow; UV_K, UV_{CL}, UV_{NA} = urinary excretion of potassium, chloride and sodium, respectively; C_{PAH} = clearance of p-aminohippurate; C_{IN} = clearance of inulin.

made up in normal saline solution, was given at a rate of 4 ml. per minute for thirty minutes before starting the first urine collection period. After three fifteen-minute urine collection periods 5 per cent saline solution was infused at a rate of 8 cc. per minute and two fifteen-minute urine collections were obtained following a fifteen-minute equilibration period. A total of four bloods were drawn at approximately equal time intervals through the course of the five urine collection periods. All urine and plasma samples were analyzed for inulin, p-aminohippurate, sodium, potassium and chloride. Inulin analyses were performed by means of Schreiner's resorcinol method,[14] p-aminohippurate by the method of Smith et al.,[15] chloride by the Schales and Schales method,[16] and sodium and potassium by means of the Perkin-Elmer internal standard flame photometer Model 52A. The Coleman Jr. spectrophotometer was used for colorimetric determinations.

An intravenous pyelogram using diodrast revealed good bilateral renal dye concentration. Both kidneys and ureters appeared normal in shape, size and position.

The results of the separate renal clearance studies are presented in Table I and the ratios of the right to left (R/L) kidney functions are graphically illustrated in Figure 1. During the control periods the glomerular filtration rate (C_{IN}) of the left kidney was 35 per cent lower than the right, the effective plasma flow (C_{PAH}) 12 per cent lower, the urine flow (V) 39 per cent lower and the sodium and chloride excretion, (UV_{NA}, UV_{CL}) 14 and 20 per cent lower, respectively. There were no significant differences between the inulin U/P ratios and the potassium excretion of both kidneys. The fraction of filtered water reabsorbed by the tubules, as represented by the inulin U/P ratios, was identical in both kidneys. During salt-loading this situation changed. Thus a transient but significant increase in renal blood flow and glomerular filtration occurred in the right kidney, not in the left. A significant increase in water, sodium and chloride excretion occurred in both kidneys. However, the output of these substances by the right kidney was respectively 90, 84 and 94 per cent higher than the left. The R/L inulin clearance ratio was 1.68 and the inulin U/P ratios on the left were significantly greater than the right, indicating increased water reabsorption on the left. During the second salt-loading period the discrepancies between the glomerular activities of the two kidneys became less marked. The R/L inulin clearance ratio dropped to 1.22 and the R/L PAH clearance ratio to 0.99. However, considerable differences in water, sodium and chloride excretion continued. The R/L excretion ratios were 1.41 for water, 1.36 for sodium and 1.38 for chloride. The R/L ratio for the inulin U/P ratios was 0.87, indicating a continued significant difference in tubular water reabsorption. The renal tubules on the left were absorbing a greater fraction of filtered water than the right renal tubules. Although the total potassium excretion increased more than twofold during salt-loading, both kidneys contributed equally to this rise.

Both kidneys had elevated filtration fractions

which rose to higher values during salt-loading. The control filtration fractions were 0.246 on the left, rising to 0.291 and 0.299 on the right, rising to 0.330 during salt-loading.

COMMENTS

The chronic elevation of left renal venous pressure experienced by this subject following a splenorenal anastomosis resulted in significant alterations of homolateral renal excretion of sodium chloride and water. Unfortunately, direct measurements of renal venous pressures were not obtained. However, since a pressure of 255 mm. of saline solution was present in one of the branches of the right gastroepiploic vein following anastomosis, it appears justifiable to assume the transmission of pressure ranging close to this value to the left renal vein through the markedly dilated splenic vein. This pressure falls within the range of renal venous pressures obtained by Maxwell, Breed and Schwartz[17] in subjects with congestive heart failure.

The discrepancies between the values obtained for C_{IN}, C_{PAH}, UV_{NA} and UV_{CL} for the individual kidneys are not explainable on the basis of random variation since individual kidney studies in subjects in whom equal function is expected bilaterally revealed such differences to be less than 10 per cent.[13,19] During the control periods the relative depression of water and salt excretion by the left kidney may be explained by the significant depression of glomerular activity on that side.[1] Without renal venous pressure measurements the contribution of active renal arteriolar resistance to this depressed glomerular function cannot be ascertained. The calculations of Maxwell et al.[17] in human congestive heart failure, Selkurt et al.[8] with artificially elevated renal venous pressures in dogs and of Bradley and Bradley[18] using abdominal compression in man indicate that increased renal venous pressure *per se* cannot entirely explain the depressed clearances under these conditions. Marked alterations of renal arteriolar tone must be postulated. The presence of elevated filtration fractions in both the homo- and ipsilateral kidneys is of interest, suggesting active vasoconstriction with relative efferent arteriolar preponderance similar to that observed in congestive heart failure.

During salt-loading the relative depression of salt and water excretion by the homolateral kidney was greater than the reduction of glomerular activity. A specific tubular alteration is suggested as a result of chronic venous congestion manifested by a relative increase in salt and water reabsorption by the congested renal tubules during salt-loading.*

Although potassium excretion increased by more than twofold during salt-loading, there was no significant difference between the excretion rates of this substance by the individual kidneys either before or after salt-loading. This observation suggests that neither chronic venous congestion nor alterations of glomerular activity significantly influence the rate of potassium excretion.

Injury to the left kidney or left renal vein thrombosis, secondary to operative manipulation, rather than increased venous pressure, may be postulated as a cause for the depressed function on that side. However, the nine-month postoperative period preceding the study, the good diodrast visualization with normal configuration and water reabsorption (inulin U/P ratios) equal to and greater than that of the right kidney militate against this interpretation. The absence of further hematemesis suggests continued patency of the anastomosis.

SUMMARY

1. Individual kidney clearances of inulin and p-aminohippurate and the ability of the individual kidneys to excrete sodium, chloride, potassium and water were studied before and during salt-loading in one subject nine months following splenorenal anastomosis for portal hypertension.

2. Prior to salt-loading the kidney subjected to increased renal venous pressure (left) presented significant relative depressions of inulin clearance, urine flow, and sodium and chloride excretion. The depressed urine and salt excretion during this period could be explained entirely on the basis of reduced glomerular activity.

3. During early salt-loading hyperemia and increased glomerular activity occurred in the right kidney, not in the left. Throughout salt-loading the relative depressions of salt and water excretion by the left kidney were significantly greater than the relative depression of glomerular function. A specific tubular effect of chronic

* Since the quantitative relationships between changes in glomerular and tubular function and changes in salt excretion have yet to be clarified, implications of glomerular or tubular responsibilities for alterations in salt excretion are purely hypothetical.[20]

venous congestion is postulated, manifested by increased water and salt reabsorption during salt-loading.

4. The filtration fractions of both kidneys were significantly elevated and became more so during salt-loading.

5. There were no significant differences in potassium excretion by the separate kidneys before and during salt-loading.

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Coexistence of Cushing's Syndrome and Internal Hydrocephalus Produced by a Cerebellar Tumor*

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It is the purpose of this paper to present a case of Cushing's syndrome coexisting with a tumor of the cerebellum. To our knowledge no such case is on record. In view of the widespread interest in the pathologic physiology of Cushing's syndrome it would seem to be of interest to present this case and discuss some of the theoretic aspects.

CASE REPORTS

F. A., a thirty-five year old white male, was admitted to the medical service in a semi-stuporous state.

The history as obtained from the family was that he had "suffered from sick headaches" for at least twenty years. Approximately two years before admission he began to complain of generalized weakness. About this time his mother noted that his face was "more round" and "quite red," and in the following year and a half he had an increase in weight from 155 to 190 pounds. Approximately seven months before admission he consulted his family physician because of increase in severity of weakness and he also complained that he could not use his left arm. He appeared awkward and it was noted that his gait was unsteady. He also complained of decreasing vision, dizziness and increase in severity of headache. The family was told that he had "high blood pressure and too many red blood cells." He was placed on a low sodium reduction diet and on this regimen his weight went from 190 to 170 pounds. His symptoms increased over the next six months so that ten days prior to admission he had been confined to bed because of weakness and two days before admission he had a generalized convulsion.

There was no history of polyuria, polydypsia, easy bruisability or renal colic. Figure 1 demonstrates the classical features of Cushing's syndrome.

The remainder of the physical examination revealed the heart to be enlarged 2 cm. beyond the mid-clavicular line in the fifth interspace. There were no murmurs and a regular sinus rhythm was present. Examination of the lungs, abdomen and genitalia showed nothing remarkable.

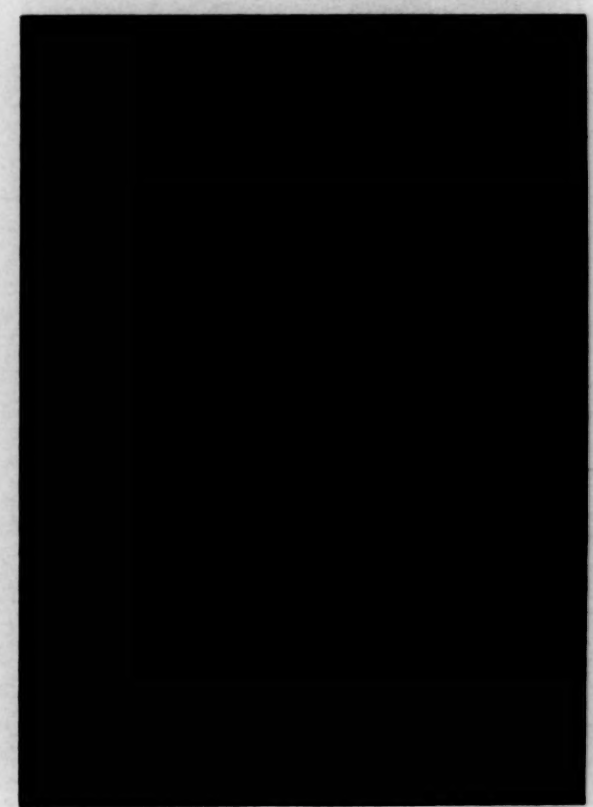

FIG. 1. Patient F. A., demonstrating body contour and striae of Cushing's syndrome.

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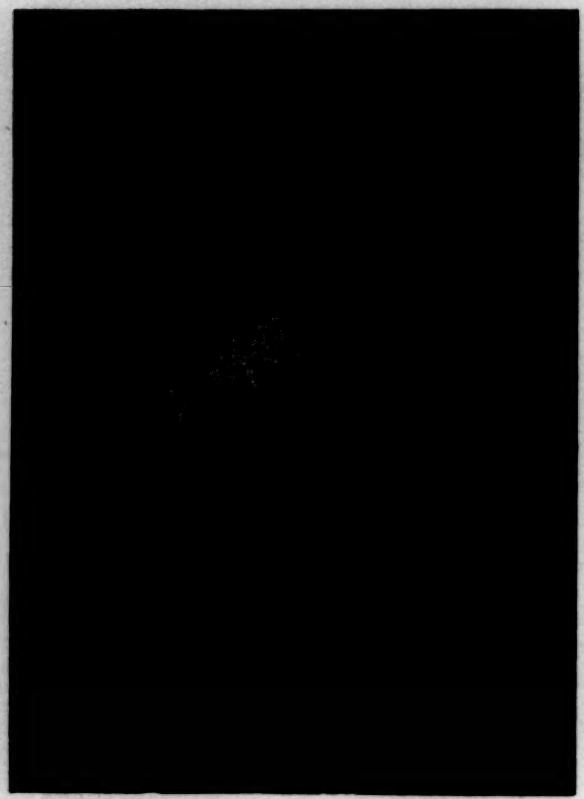

FIG. 2A

FIG. 2B

FIG. 2. A, ventriculogram, anteroposterior view, demonstrating enormous symmetrical dilation of the ventricular system; B, ventriculogram, lateral view, demonstrating dilatation of the ventricular system and the absence of air in the fourth ventricle.

Neurologic examination revealed the deep tendon reflexes to be equal but slightly hypoactive bilaterally. The pupils reacted sluggishly to light and fundoscopic examination revealed bilateral choked discs with hemorrhages and exudate. There were central paresis of the seventh nerve on the right and nystagmus on lateral gaze bilaterally.

Laboratory examination on admission revealed the following: red blood cells 5.2 million, hemoglobin 15.5 gm., hematocrit 49 per cent and white blood cells 13,000. Urinalysis: specific gravity 1.017, acid, albumin and sugar negative. Microscopic examination showed an occasional red blood cell. X-ray examination of the skull was reported as normal. X-ray examination of the chest showed minimal cardiac enlargement.

The neurosurgical consultant performed ventriculograms which revealed "enormous symmetrical dilatation of the ventricular system, no air in the 4th ventricle." (Fig. 2.) Operation was promptly performed.* The posterior fossa was explored through a sub-occipital incision.

* Operation performed by Dr. Juan Martinez and Dr. William Ledyard of the Department of Neurosurgery, University of Virginia, Charlottesville, Va.

The following was recorded in the operative notes: "A ventricular needle was passed into the left cerebellar hemisphere and encountered abnormal tissue. A small biopsy was taken. The cerebellum was retracted and at the level of about 1 cm. in depth, tumor tissue was encountered. A large amount of the tumor was removed by suction. By this time, the block of the fourth ventricle had been removed. The patient left the operating room in fair condition."

The pathologic report was as follows: "There is a small amount of tissue consisting almost entirely of mature astrocytes. This represents a tumor, the cells of which have very little cytoplasm; nuclei are uniform, dark and oval. The stroma is formed by the cell processes composing a dense fibrillary network. Final Diagnosis: Astrocytoma."

The patient did well postoperatively and on the seventeenth postoperative day was transferred back to the medical service for further diagnostic studies. At this time he was alert but seemed to be somewhat confused. Otherwise his general appearance was not significantly different from the time of admission to the hos-

pital. The blood pressure was 140/120. He no longer complained of headache.

Additional studies included a blood urea of 24 mg. per cent, serum chlorides 93 mEq./L., CO_2 combining power 29.5 mEq./L., serum calcium 9.0 mg. per cent, serum phosphorous 2.4 mg. per cent, alkaline phosphatase 2.7 Bodansky units, serum albumin 3.8 gm. per cent, serum globulin 2.4 gm. per cent, serology negative. A five-hour glucose tolerance test was reported as follows:

	Sugar	Urine
Fasting (hr.)	100 mg. %	0
1	238	0
2	213	2+
3	167	2+
4	63	0
5	95	0

On the nineteenth and twentieth postoperative days endocrine studies revealed the following: a total eosinophil count was 9/cu. mm., the 17-ketosteroid excretion was 21.6 and 19.2 mg. per twenty-four hours (Normal: 10–25 mg. per twenty-four hours), the urinary "cortins" were 7.6 mg. per twenty-four hours (Normal: 0.5–2 mg. per twenty-four hours).

An intravenous pyelogram was not entirely satisfactory but revealed normal excretion and no distortion of the renal shadows. An interesting finding was marked calcification of the pelvic vessels. X-ray of the thoracolumbar revealed no x-ray evidence of osteoporosis.

There was no evidence of abnormal water exchange and the temperature was normal.

The patient was discharged on the twenty-first hospital day in fair condition to be followed by his local physician.

COMMENT

All of the features of Cushing's syndrome have now been produced in man with the administration of either cortisone, compound F or ACTH in large doses. Albright and others[1] have reviewed the evidence indicating that Cushing's syndrome is due to hyperadrenocorticism, and this in turn may be due to a tumor of the adrenal cortex or to bilateral adrenal cortical hyperplasia. The mechanism in these latter cases which results in an overproduction of "cortisone like" steroids remains to be established.

At the present time there is a great deal of interest in the possible relationship of the hypothalamus to pituitary and adrenal function. Recently Hume and Wittenstein[3] have presented studies of hypothalamic stimulation in dogs. A small coil placed in the hypothalamic area of the dog may be stimulated by bringing a large primary coil close to the dog's head with the dog fully conscious. Stimulation of the hypothalamus by this method causes a marked fall in eosinophils and a concomitant leukocytosis. This was interpreted as evidence for hypothalamic control of pituitary release of ACTH. Heinbecker has presented clinical and experimental studies[4] attempting to show that the "primary disturbance" in some cases of Cushing's syndrome is due to atrophy of the paired paraventricular nuclei of the hypothalamus. He has reported two cases of Cushing's syndrome coexisting with proven intracranial disturbance. The first patient had a meningioma in the region of the second cervical vertebra with a complete block of her spinal canal in this area; following removal of the tumor, there was disappearance of the signs and symptoms of Cushing's syndrome. The second patient presented evidence of increased intracranial pressure for seven years before the development of the clinical picture of Cushing's syndrome.

We know that our patient had increased intraventricular pressure as shown by the ventriculograms. From the history the precise time relationship between the development of the increased intracranial pressure and the manifestations of Cushing's syndrome is not clear. However, it seems reasonable to postulate that pressure in the third ventricle may have caused hypothalamic stimulation with the release of ACTH from the pituitary. A cogent argument against this hypothesis is the fact that one sees many patients with increased pressure in the third ventricle caused by brain tumors, meningitis, etc. who present no signs or symptoms of Cushing's syndrome.

Four months postoperatively the patient has no change in the Cushing's syndrome. In the event that the Cushing's syndrome clears up, it might be construed as evidence in favor of the concept that increased pressure in the third ventricle caused by the cerebellar tumor was an etiologic factor in the production of Cushing's

syndrome. On the other hand, persistence of this syndrome would not rule out this hypothesis since it is not unlikely that the increased intracranial pressure had produced irreversible structural alterations in the hypothalamus.

SUMMARY

A case history is presented of a patient who had a cerebellar tumor resulting in block of the ventricular system with marked internal hydrocephalus. He presented in addition the classical picture of Cushing's syndrome. The possibility that hypothalamic damage may have resulted in Cushing's syndrome is considered.

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heart disease 42%

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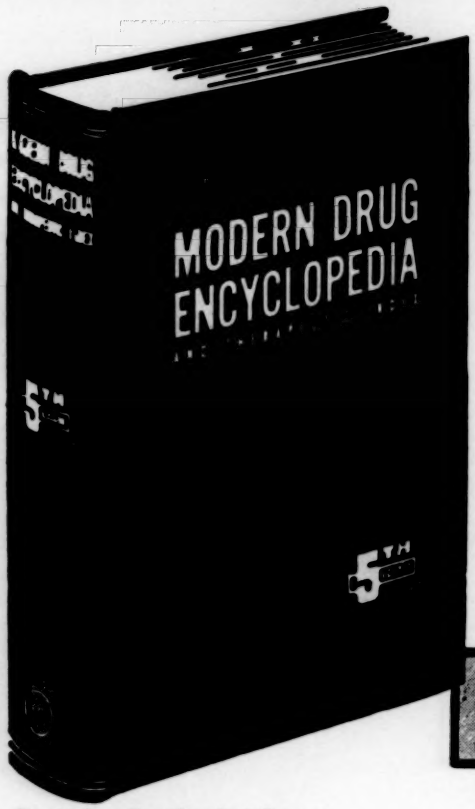

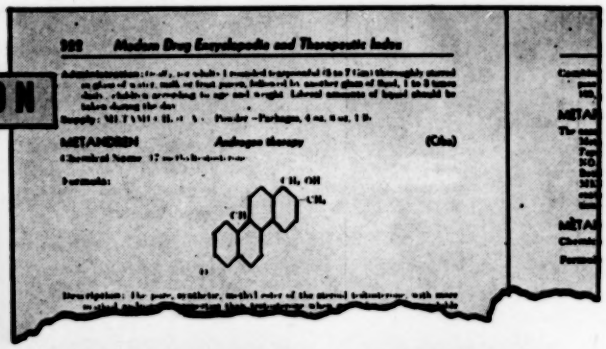

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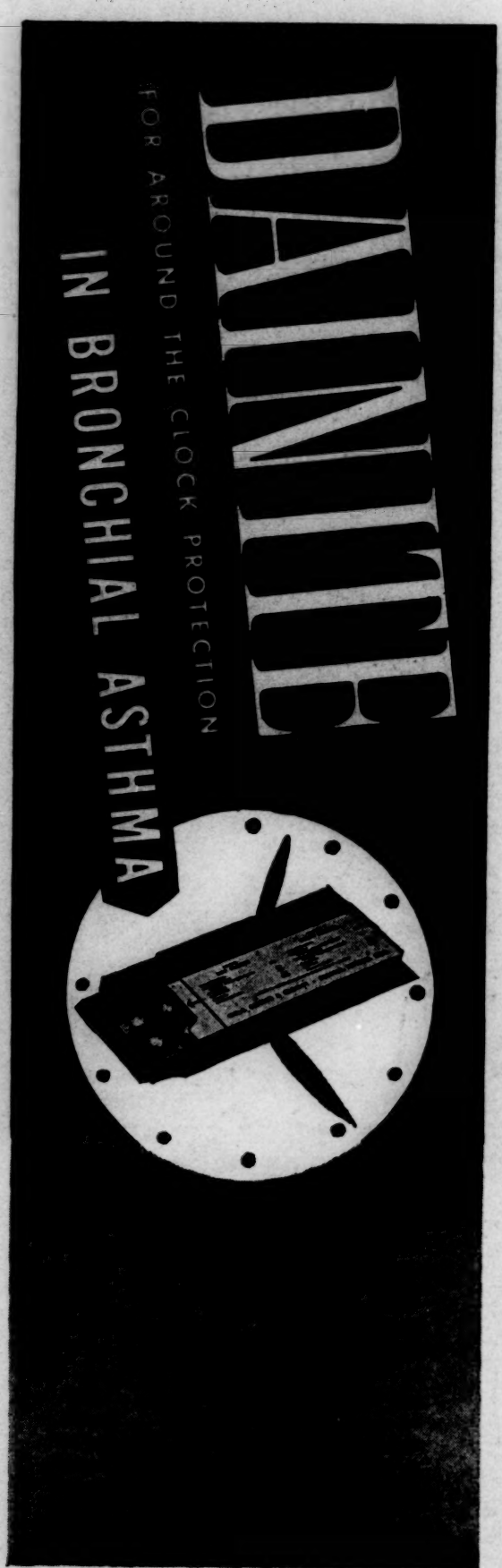

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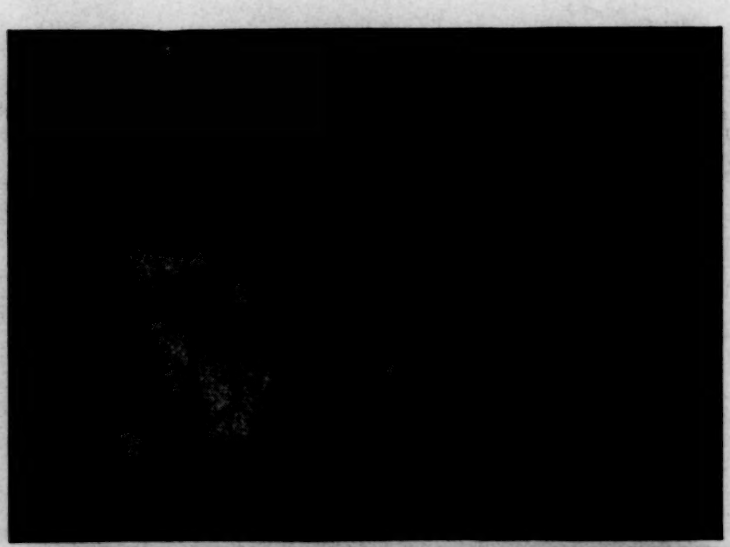

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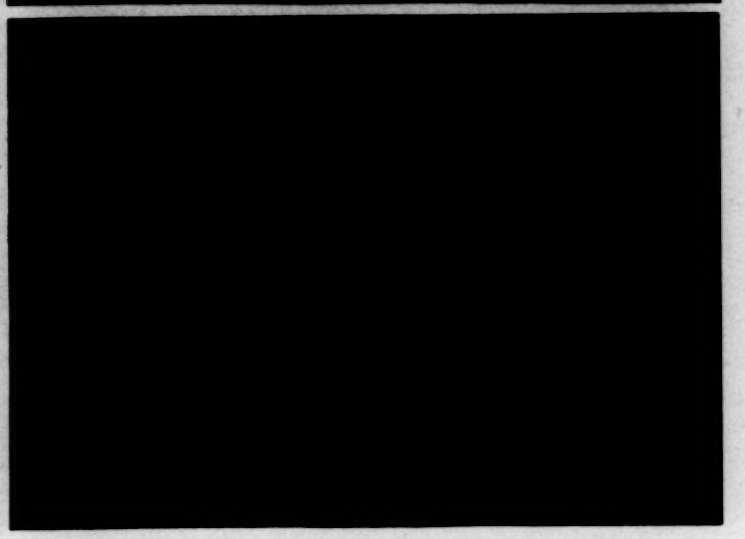

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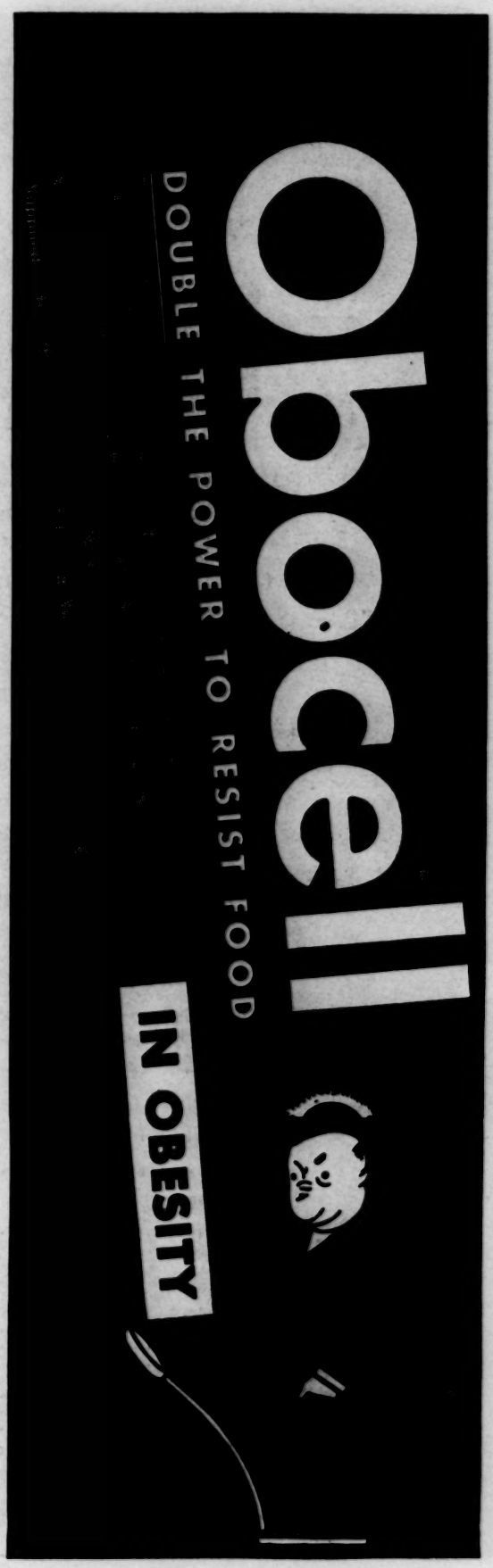

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